HYDROGELS FOR DERMAL APPLICATIONS

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Doctor of Philosophy

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- Chapter 1 -

THESIS SUMMARY ASTON UNIVERSITY

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This thesis is concerned with the development of hydrogels that adhere to skin and can be used for topical or transdermal release of active compounds for therapeutic or cosmetic use.

The suitability of a range of monomers and initiator systems for the production of skin adhesive hydrogels by photopolymerisation was explored and an approximate order of monomer reactivity in aqueous solution was determined. Most notably, the increased reactivity of *N*-vinyl pyrrolidone within an aqueous system, as compared to its low rate of polymerisation in organic solvents, was observed. The efficacy of a series of photoinitiator systems for the preparation of sheet hydrogels was investigated. Supplementary redox and thermal initiators were also examined. The most successful initiator system was found to be Irgacure 184, which is commonly used in commercial moving web production systems that employ photopolymerisation.

The influence of ionic and non-ionic monomers, crosslinking systems, water and glycerol on the adhesive and dynamic mechanical behaviour of partially hydrated hydrogel systems was examined. The aim was to manipulate hydrogel behaviour to modify topical and transdermal delivery capability and investigated the possibility of using monomer combinations that would influence the release characteristics of gels by modifying their hydrophobic and ionic nature. The copolymerisation of neutral monomers (*N*-vinyl pyrrolidone, *N,N*-dimethyl acrylamide and *N*-acryloyl morpholine) with ionic monomers (2-acrylamido-2-methylpropane sulphonic acid; sodium salt, and the potassium salt of 3-sulphopropyl acrylate) formed the basis of the study.

Release from fully and partially hydrated hydrogels was studied, using model compounds and a non-steroidal anti-inflammatory drug, Ibuprofen. Release followed a common 3-stage kinetic profile that includes an initial burst phase, a secondary phase of approximate first order release and a final stage of infinitesimally slow release such that the compound is effectively retained within the hydrogel. Use of partition coefficients, the pKa of the active and a knowledge of charge-based and polar interactions of polymer and drug were complementary in interpreting experimental results. In summary, drug ionisation, hydrogel composition and external release medium characteristics interact to influence release behaviour. The information generated provides the basis for the optimal design of hydrogels for specific dermal release applications and some understanding of the limitations of these systems for controlled release applications.

For Mamma, with love.

"To live in hearts we leave behind is not to die"
(Thomas Campbell, 1777-1844)

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Abbreviations

°C	degrees centigrade
C_{di}	concentration of solute, i, in donor phase (mol/cm^3)
C_{ri}	concentration of solute, i, in receptor phase (mol/cm^3)
CL	contact lens
D	diffusion
DC_i/d_z	concentration gradient
D_i	diffusion co-efficient of solute i (cm^2/s)
EWC	equilibrium water content
g	grams
G'	elastic modulus
G"	viscous modulus
G*	complex modulus
HPLC	high performance liquid chromatography
Hz	Hertz
i	solute
j_i	flux of solute i (mol/cm^2)
K_i	partition co-efficient of solute
K (o/w)	water:octanol partition co-efficient
KV	kilovolts
L	membrane thickness (cm)
MeOH	methanol
mg	milligrams
mol	Moles
ml	millilitres
mm	millimetres
MW	molecular weight
µl	microlitres
µm	micrometres
P	permeation
Pa	Pascals
PBS	phosphate buffered saline

pH	is the negative log of the concentration of H^+ ions
P_i	permeability of solute, i (cm^2/s) = K_iD_i
PI	photoinitiator
pKa	constant describing the ionisation of an acid
ppm	parts per million (measure of concentration)
N	Newtons
O/N	overnight
s	solubility
SEM	scanning electron microscope
UV	ultra violet
w/w	weight:weight ratio

For chemical abbreviations see table 2.1

Chapter One

Introduction

1 Introduction

1.1 Hydrogels as Biomaterials

Hydrogels are covalently-crosslinked hydrophilic polymer networks, of either natural or synthetic origin, which can absorb and retain a considerable fraction of water within their structure, without dissolution and loss of structural integrity. They can be classified in a number of ways according to chemical and physical structure, and method of preparation, as shown in table 1.1.

Basis of Classification	Classes of Hydrogels	Description
Preparation	Homopolymer	One type of hydrophilic monomer
	Copolymer	Two types of monomer; one must be hydrophilic
	Multi-polymer hydrogel	Three or more monomers; one must be hydrophilic
	Interpenetrating network hydrogel	One crosslinked polymer is swelled in a second monomer that is reacted to form second intermeshing network
Ionic charge	Neutral	No charge
	Anionic	Negatively charged
	Cationic	Positively charged
	Ampholytic	Capable of behaving positively and negatively
Physical & structural features	Amorphous	Randomly ordered polymer chains
	Semicrystalline	Contains dense regions of ordered polymer chains
	Hydrogen-bonded	Three-dimensional network held together by hydrogen bonds

Table 1.1 Classifications of hydrogels

Since their initial development for use as soft contact lens materials in 1960, hydrogels have become a diverse and widespread group of materials in the biomedical field. Current applications include contact lenses and other ocular prostheses, bioelectrodes, drug delivery systems, synthetic articular cartilage analogues, wound dressings and biosensors. Some examples of commercially available hydrogel devices are shown in figure 1.1.

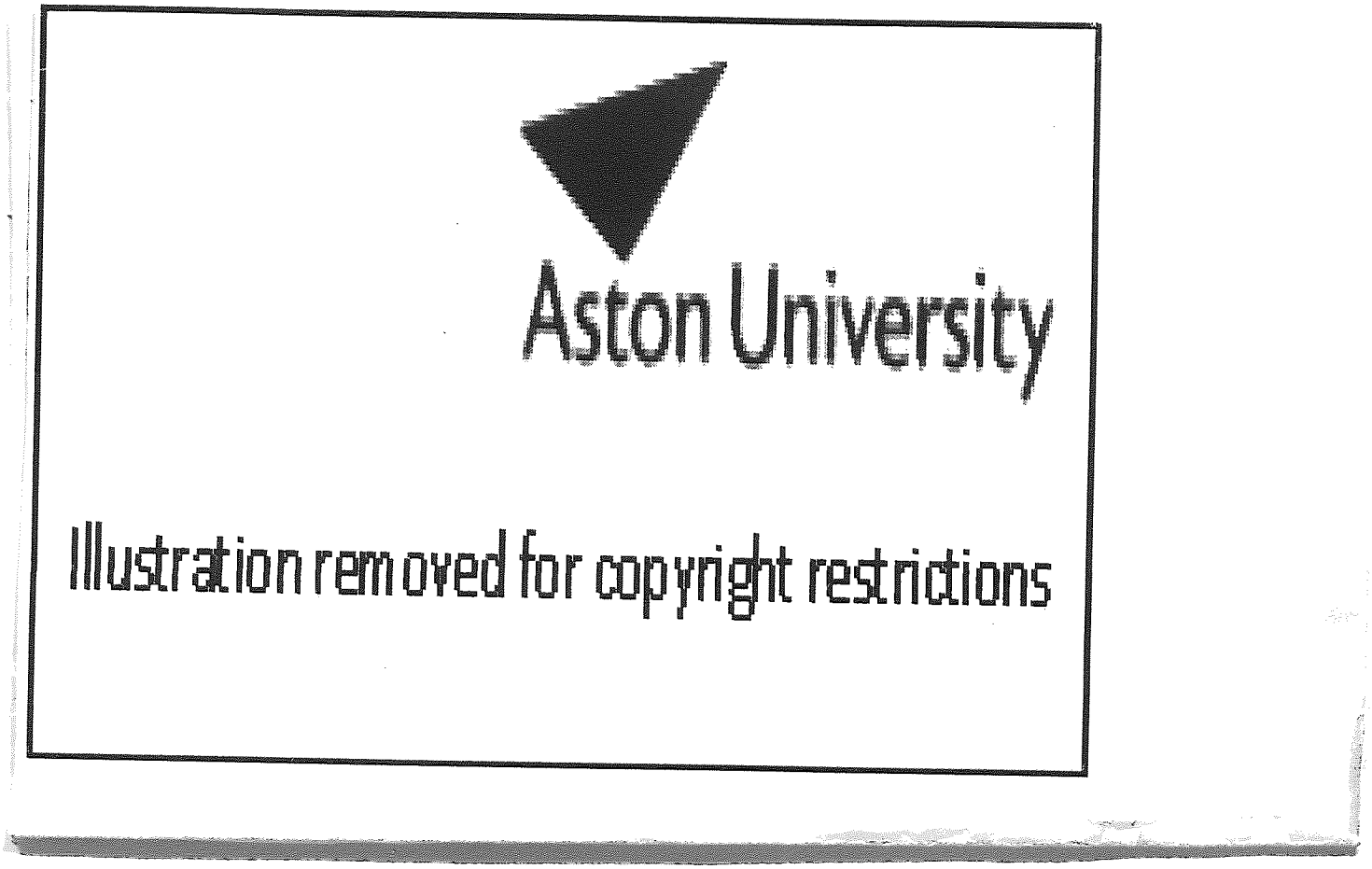


Figure 1.1 Examples of commercial hydrogel devices
(First Water Hydrogels Ltd)

Current developments and interest in the use of hydrogels in biomedical applications stem from the work of Otto Wichterle and his colleagues. In the early 1960s research by the group produced patents indicating the application of lightly cross-linked 2-hydroxyethyl methacrylate (HEMA) (see Fig 1.2) hydrogels in soft contact lenses (Wichterle et al, 1960).

Figure 1.2 Structure of HEMA

The compatibility of this material with living tissues, coupled with its stability under the varying conditions of tonicity, pH and temperature seen in the body, made it an ideal candidate biomaterial. For many years pHEMA has subsequently been seen as an epitome for the study of structure property relationships in hydrogels, and it is only in the last 20 years or so that the potential of other hydrogel compositions for use in the biomedical field has been more thoroughly investigated. As our understanding of this class of materials increases, new monomers are being introduced and the extent and ratio of co-polymerisation of monomers is being engineered to produce hydrogels with characteristics tailored to suit specifically a broad range of intended applications.

1.2 Hydrogel Synthesis

Hydrogels are produced by the co-polymerisation of hydrophilic monomers, in the presence of small concentrations of initiator, with small concentrations of multifunctional cross-linking agents, to produce hydrophilic networks of cross-linked polymer chains. These networks are capable of absorbing up to thousands of times their own weight in water to become elastic water containing gels (Hoffman, 2002). The constituent monomers within a hydrogel determine the functional groups branching from the carbon atom backbones of the polymer chains within the gel. The primary function of these chemical groups is to attract and bind water within the material. By changing the composition of a hydrogel, the degree to which the hydrogel can become water-swollen (its equilibrium water content) can be altered to modify the material's chemical and mechanical properties to suit a particular application.

The kinetic mechanism for co-polymerisation/crosslinking (figure 1.4) begins with the initiation of polymerisation by promotion of an outer electron of the initiator species to a higher orbital and thus an electronically excited state, by the application of an external energy source. This unstable species now rapidly reacts to re-establish its preferred stable state. This is achieved either by decaying of the initiator back to its original state, the excess energy being emitted as light or heat, or by its taking part in a chemical reaction yielding a reactive intermediate such as a free radical. These free radicals form longer free radical chains with unsaturated monomers. This chain-reaction for the production of reactive intermediate species means that only very small quantities of initiator are required for propagation of polymer chains. Each chain propagation can be terminated by combination of two radicals to form a final molecule, disproportionation of the radical chain ends by transfer of a hydrogen atom, or by completion of the polymerisation. As termination is a random process the resultant polymer chains vary in length. The multifunctional crosslinking monomer covalently bonds with pendant hydroxyl groups on the polymer chains and the polymer backbones themselves to produce a three-dimensional crosslinked polymer network.

Initiation $I \rightarrow R\bullet + R\bullet$

Propagation
$$\begin{cases} R\bullet + M \rightarrow RM\bullet \\ RM\bullet + M \rightarrow RMM\bullet \\ RMM\bullet + nM \rightarrow RMM(M)n\bullet \end{cases}$$

Termination $RMM\bullet + RMM\bullet \rightarrow RMMMMR$

Where I = initiator, R = radical, M = monomer, and • = reactive species

Figure 1.3 Schematic representation of the steps involved in a polymerisation reaction.

The oldest, simplest method for polymerisation uses thermal energy and is frequently used in the production of contact lenses and other small devices, because of its versatility and relative low expense. Thermal polymerisation requires relatively long periods of time and large production areas however, making it unsuitable for the bulk production of large articles. Photopolymerisation, a modern alternative that uses light as an energy source, allows rapid, continuous production of bulk quantities of hydrogels such as large uncovered sheets of skin adhesive hydrogels that are subsequently covered with a backing paper and cut to the required shape and size. Photo-initiator agents absorb UV light in the visible spectral range (250-450nm) and rapidly convert it into chemical energy in the form of free radicals, which is then used by photo-crosslinking agents to initiate the formation of new chemical bonds (Oster, 1990). This technique is associated with lower monomer/solvent emissions and facilitates the use of heat sensitive substrates, such as the actives incorporated into some hydrogel dressings.

To ensure production of a hydrogel with consistent bulk and surface properties, photopolymerisation must be uniform. This in turn requires uniform initiation and production of the reactive species described previously. Problems often occur in ensuring adequate and equivalent polymerisation of the surface and bulk of the hydrogel. Initiator decomposition is greatest at the surface of the gel because of the greater light intensity there. As optical density increases through the deeper layers of a sample cure of the lower layers of the gel is hindered. In contrast, a major problem encountered during the photopolymerisation of hydrogel sheets is air inhibition of complete polymerisation at

the hydrogel surface. Presence of oxygen species at the gel surface can reduce the number of reactive species available for polymerisation by either deactivating or reacting with them. Although increasing photo-initiator concentration provides a potential solution to the problem of complete surface cure the accompanying increase in optical density and reduction in light absorbance in the lower layers again hinders uniform polymerisation. In certain circumstances air inhibition may be eliminated by polymerising the gel in either a vacuum or in the presence of an inert gas. However, in the case of skin adhesive hydrogel membranes, the large increase in production costs and impracticalities of producing the gels in this way, make this technique unsuitable.

1.3 Water in Hydrogels

1.3.1 Equilibrium Water Content of Hydrogels

The Equilibrium Water Content (EWC) of a hydrogel is its single most important property as it is this water that gives hydrogels the unique properties that favour their use as biomaterials. The water held by the polymer affects the biocompatibility, mechanical properties and surface properties of the gel, acting as a transport medium for dissolved oxygen and protein/peptide molecules found in extracellular fluid, a plasticizer, and a "bridge" between the different surface energies of the polymer and body fluids respectively (Corkhill et al,1990).

The EWC of a hydrogel is defined and is usually calculated as shown below:

$$EWC = \frac{weight\ of\ water\ in the\ gel}{total\ weight\ of\ hydrated\ gel} \times 100\%$$

However, as the water present in the hydrogel affects the density and refractive index of the polymer, measurement of these properties may also be used to determine EWC (Corkhill et al, 1990).

The EWC of a hydrogel is determined by internal factors such as the nature and quantity of the constituent hydrophilic monomers, and the nature and density of any cross-linking agent(s). Whilst the hydrophilic network is osmotically driven towards infinite dilution, the covalent crosslinks between the polymer chains oppose such a degree of swelling, creating an elastic network retraction force. Together these dictate an equilibrium swelling point of the hydrogel (Hoffman, 2002).

EWC is further affected by external environmental factors such as temperature, pH and tonicity of hydrating medium (Pedley et al, 1980). The effect of temperature on the EWC and therefore the dimensions of hydrogels are important in consideration of their use in a wide range of biomedical applications. Variations in the size and water content of the hydrogels, from room temperature to body temperature and at the higher temperatures necessary in sterilisation of the gels prior to their use and the consequences of these for

their suitability for specific applications must be considered. Any increase in temperature leads to a decrease in what is sometimes referred to as hydrophobic hydration, and an increased formation of hydrophobic bonds. These bonds are Van der Waal interactions between non-polar groups, which act as cross-links within the polymer matrix, reducing free space and thus the EWC of the hydrogel. However, hydrophilic hydration, the formation of hydrogen bonds between polar groups of the polymer and water in the hydrating medium, increases with increasing temperature. The polymer network expands entropically leading to an increased capacity for the hydrogel to absorb water (Corkhill, 1990).

1.3.2 Volume Fraction of Water within Hydrogels

Many hydrogels become adhesive when hydrated and their degree of adhesivity is affected by the volume fraction of water within the gel. The partial hydration of the gel and its associated swell allows a greater degree of rotation of the polymer chains whilst maintaining the gel's high residual capacity for water uptake. As a result, partially hydrated, high EWC hydrogels are particularly adhesive to moist soft tissue. This property is exploited in a number of biomedical applications of hydrogels such as wound dressings and electrodes. Control of both equilibrium water content and degree of hydration of a hydrogel can be used to modify the physical properties and adhesive behaviour of the hydrogel under specific conditions.

1.3.3 Water-structuring within hydrogels

Independent of the EWC, water structuring within a hydrogel is also an important influence on the properties of hydrogels. Though there is dispute concerning the nature and number of states of water within hydrogels, it has been suggested that the water exists in a continuum between two extreme states of "bound" and "free" water. When a hydrogel is first hydrated the water primarily binds to the most polar, hydrophilic groups. Consequent swelling of the polymer network exposes hydrophobic pendant groups that bind hydrophobically with the water. These primary and secondary bound water states are grouped together as total bound water. Osmotically driven water that subsequently

swells the gel, filling the spaces between the crosslinked network chains is known as free water (Hoffman 2002). The elastic network refraction force, which limits this swelling, is controlled by the crosslinks within the polymer network. As crosslink density increases, increased steric occlusion of hydrophilic binding sites and decreased mobility within the polymer network greatly reduce the free water content. The ratio of bound and free water is thought to play a central role in determining the surface, transport, and mechanical properties of hydrogels.

Several methods are available which give information on the structuring of water in hydrogels; the most frequently used being Differential Scanning Colorimetry (DSC) which gives details of the relative proportions of the two extreme states of water mentioned. Since the method used can influence the dynamic and thermodynamic properties of the water in the hydrogel and the states into which it is classified all currently available methods are subject to some controversy.

1.4 Mechanical Properties

1.4.1 Effects of crosslink density

Hydrogels derive most of their physical strength from physical crosslinks within the material that form a network of the polymer chains. By using higher concentrations of crosslinking agent in hydrogel synthesis, crosslink density can be increased, dramatically increasing the mechanical strength of the gel. It is important to consider, however, that this is likely to be accompanied by changes to other properties of the material. Diffusion within the gel will be impeded by additional crosslinks, resulting in reduced swell and release rates, and the EWC of the hydrogel will be lowered due to an increased elastic network refraction force. At a crosslink density specific to a particular hydrogel composition, these effects will be such that the material synthesised does not behave as a "gel", instead possessing the properties of a glassy plastic (Corkhill et al).

1.4.2 Interpenetrating Networks (IPNs)

Although the water present in a hydrogel is vital for its influence on many of the properties that make these materials suitable for use in medical applications, it can impart adverse changes in the mechanical strength of the gels. To compensate for the effects of water on mechanical strength, polymer blends known as interpenetrating networks (IPNs) can be used to create hydrogels with structures that provide much greater mechanical strength whilst still accommodating high water contents.

IPNs can be defined as a combination of two polymers, each in network form, at least one of which has been synthesised and/or crosslinked in the presence of the other. They can be divided into three classes depending on their method of synthesis.

Sequential IPNs are produced by polymerising and crosslinking monomer I, swelling it in monomer II/crosslinker/initiator mix and polymerising and crosslinking this second monomer around monomer I.

Simultaneous IPNs involve polymerisation of a blend of two monomers such that both monomers are polymerised at the same time but by different non-interfering methods.

The third class of IPNs concerns those polymer composites where only one of the two monomers is crosslinked. A pre-polymerised linear polymer is dissolved in a second monomer and the solution then polymerised to crosslink the second monomer around the first. These polymers are known as semi-IPNs (Sperling, 1981). Figure 1.4 (below) shows a schematic representation of the possible two-polymer combinations of IPNs.

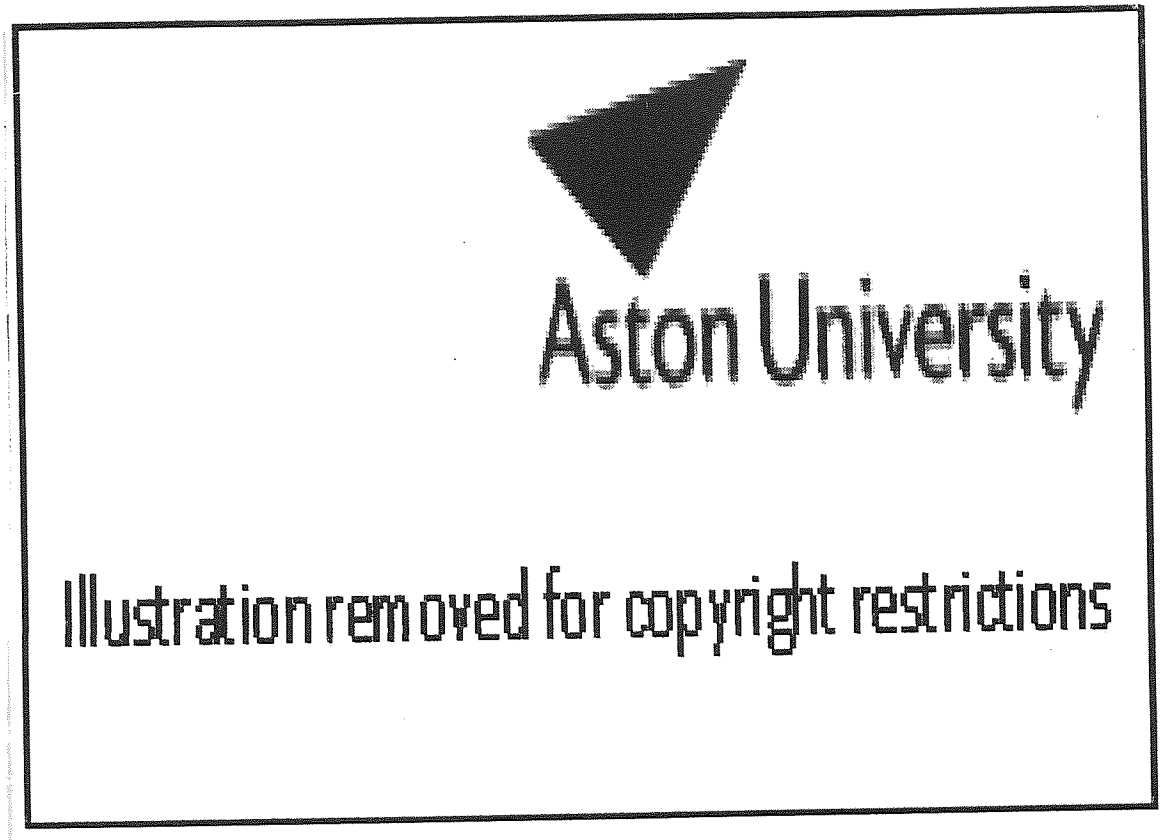


Figure 1.4 Showing possible two-polymer combinations
(a) polymer blend, (b) graft copolymer, (c) block copolymer, (d) semi-IPN, (e) full IPN, (f) AB crosslinked polymer. (Corkhill 1990)

Interpenetrating polymer networks allow modification of hydrogel properties to combine desirable properties of two monomers, for example the high strength of one monomer with the water-binding properties of another. In a manner similar to that seen in biological composite hydrogels however, IPNs enhance the strength and stiffness of the gels at the expense of their elasticity. Further research with IPNs in this area may eventually enable the design of synthetic hydrogels that closely mimic their naturally occurring counterparts (biomimetic) to produce superior prosthetics.

1.4.3 Measurement of Mechanical Properties of Hydrogels

Accurate measurement of mechanical and surface properties of hydrogels is difficult, partly due to the inherent properties of the gels and mainly because of loss of water from the gel during measurements taken in a non-aqueous environment. Loss and re-distribution of water, through evaporation and mechanical deformation, during the measuring techniques that are currently available means that values measured are rarely of accurate quantitative value but can be a useful source of comparative data. Mechanical and surface measurements provide information about the likely behaviour of a hydrogel under application-specific conditions and can be used to define acceptable ranges for different material parameters and to assess the suitability of a hydrogel for an application.

1.5 Adhesive Hydrogels

1.5.1 Theories of Adhesion

Adhesion can be defined as the state in which an interface is formed between two bodies such that molecular forces across the interface resist separation for an extended period of time (Bateup 1981). When one or both of the adherends are of a biological nature this interaction is known as bioadhesion. This phenomenon almost always occurs in the presence of water and thus, it is often seen that bioadhesives demonstrate poor adhesive characteristics in dry conditions. (Park et al, 1986). The adhesion of an artificial substrate such as a hydrogel to a biological substrate is further classified as Type III adhesion (Park et al, 1986).

Peppas and Mikos described bioadhesion as a "phenomenon rather than a mechanism- where one or more theories could equally well explain the formation of a bioadhesive bond. The applicability of each theory is not unique and should depend upon the particular system concerned."

It is proposed that three main component factors work together to influence the suitability of a hydrogel as a skin adhesive material: the rheological properties of the gel, the presence of a hydrophilic component, and short-range interactions via hydrophobic domains on flexible sidechains of the hydrogel.

Rheological Properties

The rheological properties of a hydrogel affect its ability to form a close fit with the skin (its compliance) and the structural stability of the hydrogel upon removal (its cohesion). Rheological measurement of the elastic and viscous components of deformation gives information on how a material is likely to behave under imposed shear stress conditions. Ideally, a skin adhesive hydrogel should have high hysteresis loss (dominant elastic forces) when low frequency stresses are applied, such as those used in the placement of the gel. This enables close moulding of the gel to the surface variations of the skin. At high frequency stresses, hysteresis loss should be low (dominant viscous component) to

minimise extension of the hydrogel during its removal (known as legging) and allow removal of the gel in one piece.

Hydrophilic Component

A hydrophilic component to the gel is necessary for the removal of the lubricating interfacial water layer between the hydrogel and the skin that might otherwise prevent maximum potential interfacial interaction (Park, 1984). The use of hydrophilic constituent monomers produces gels with polymer sidechains containing hydrophilic groups such as hydroxyl, carboxyl and polar groups. By applying the hydrogels to the skin in a partially hydrated state, these groups maintain a high residual capacity for water uptake (the hydrogel has a high potential EWC) promoting adhesivity of the gel to the skin.

Hydrophobic Domains

Once intimate contact between the hydrogel and skin has been established, short range interactions such as hydrogen-bonding, Van der Waals attractions and other forces contribute significantly to adhesive strength (Park, 1984). The low crosslink density of hydrogels compared with that seen in other polymers allows the external hydrogel chain branches (of hydrated hydrogels) to be flexible. This allows the polymer chains to match their active adhesive sites with those on the substrate to form adhesive bonds (Park, 1984). In environments of relative hydrophobicity compared to that within the gel, such as in air, these groups have a tendency to rotate to expose their hydrophobic sidechains. Hydrophobic interaction of the hydrophobic functional groups of the sidechains with the hydrophobic lipids and proteins of the skin plays a major role in skin adhesion. In relatively hydrophilic external environments, such as water, the chains tend to flip to expose their polar functional groups, such as hydroxyl (-OH), carboxyl (-COOH) and sulphate groups ($-SO_4^{2-}$) to form dipolar and hydrogen bonds with hydrophilic groups on the skin (Park 1984).

Molecular weight of the adhesive, crosslink density, hydration, applied force, contact time and temperature have all been shown to affect strength of adhesion. By controlling the surface chemistry of the hydrogel, molecular contact and interactions at the interface

between the skin and the gel can be maximised. Conventional adhesion theory suggests that the surface energy of the gel must be less than or equal to that of the adherend, in this case the skin, so that the gel can effectively "wet" the skin and form intimate contact. Many studies have attempted to demonstrate this relationship but there has been insufficient correlation to support the theory (Park, 1984).

1.5.2 Hydrogels as Skin Adhesives

Depending on their intended use skin adhesive hydrogels must be able to adhere to the skin for between 24 hours and seven days. Ease of application and removal of the gel, and the maintenance of adhesivity after removal for repositioning is vital. With this in mind the hydrogel should have sufficient mechanical strength to remain cohesive should removal and repositioning be required. Increased crosslink density can be used to improve mechanical strength however this reduces sidechain flexibility, which plays an important role in accommodating the short-range interactions which promote skin-adhesion. This problem can be avoided by the addition of a water-soluble interpenetrant polymer, which acts as a plasticizer, increasing the flexibility of the gel and consequently molecular contact at the interface, without the need to compromise the mechanical strength of the gel by reduction of crosslink density.

Skin adhesives for use as sensors or electrodes must also be electrical conductors. This can be achieved simply by the use of ionic monomers/salts, whilst the presence of water within the polymer matrix eliminates the need for addition of a conduction fluid. Unlike the hydrogels used in the manufacture of contact lenses, there is no need for skin adhesive hydrogels to be transparent, but aesthetically pleasing materials hold obvious appeal. For all applications, the hydrogel must be disposable, facilitate production of sterile samples to allow effective eradication of pathogens and have sufficient shelf-life to be an economically viable product.

1.6 Composition of Skin

1.6.1 Anatomy and Physiology of Skin

The skin is the largest organ of the human body, comprising some 10% of total body mass and covering an area greater than two square metres in the average adult (Odland, 1974). Continuous growth of new cells and sloughing off of dead outer cells means that the skin is completely renewed every few weeks to optimise the protective physical barrier it provides against pathogens, radiation and chemicals from the external environment. An integral circulatory and evaporation system satisfy the thermal regulatory demands of the human body and an extensive neuroreceptor network transmits environmental information (Odland, 1974).

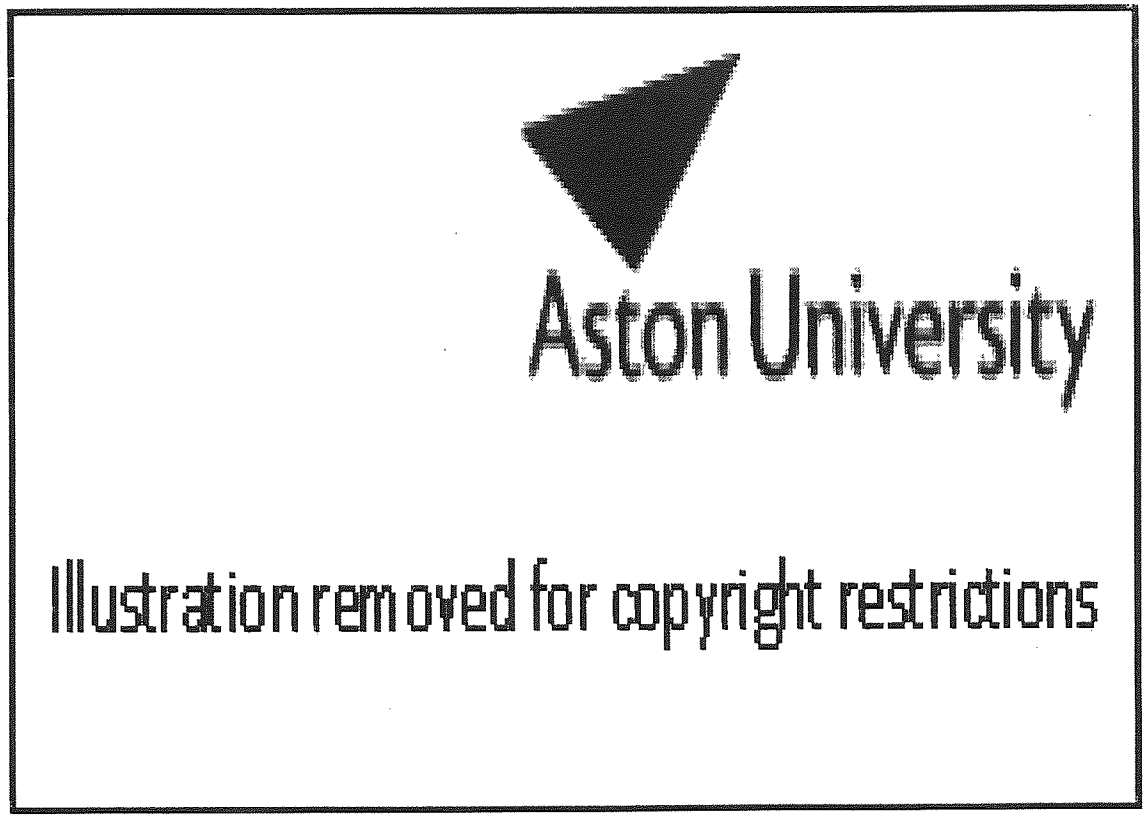


Figure 1.5 Composite representation of the structure of the integument found in typical skin in various regions of the body.
(Hobson, 1991)

The skin consists of two main layers; an inner connective layer called the dermis and an outer epithelium, the epidermis. The connective tissue of the dermis is made up mainly of dense collagen and elastin fibres, which give the tissue strength and elasticity respectively. In deeper layers and in the loose connective tissue beneath the dermis many clusters of fat cells are also present (Rogers, 1992). Through this tissue run numerous lymphatics, specialised nerves and blood vessels, the latter of which supply both the dermis and the epidermis and are pivotal in the regulation of skin temperature (Sherwood, 1997). In most areas the dermis is only loosely attached to the underlying loose connective tissue, to allow the skin freedom of movement over the muscles and bones, but at specific sites the dermis is attached more tightly to the underlying tissues. It is this and variations in the orientation of the collagen fibres of the dermis which result in the characteristic patterns of creasing seen at sites of low mobility skin such as the flexure lines of joints (Rogers, 1992).

At the interface between the dermis and epidermis the layers project into one another to create an irregular junction. Conical dermal papillae containing specialised nerve endings and capillary loops dip into the epidermis here (Moffat, 1993). As the epidermis has no blood supply of its own, it is diffusion of nutrients across this interface that nourishes the epidermis (Sherwood, 1997). Where the epidermis dips into the dermis at this junction, structural changes in the epidermis produce hair follicles, sebaceous glands and sweat glands. The presence of these structures can interfere with the mechanisms of hydrogel skin-adhesion and make the intended body site for use of a skin-adhesive hydrogel an important consideration in the design specifications of the hydrogel.

The non-vascular outer epidermis of the skin is of great interest with respect to skin adhesive hydrogels, as it is this layer that comes into contact with the gels. It consists of five subsidiary layers of stratified squamous epithelium, each of varying maturity and with slightly different characteristics (figure 1.6). The deepest layer, the *Stratum basale* is where the majority of mitoses of the skin are found as the cube-shaped keratinocytes of this layer rapidly divide to form new skin cells to replace those of the outer layer that have been sloughed off (Moffat, 1993). The prickle cells of the next layer, the *Stratum spinosum*, are more widely spread but remain strongly linked via desmosomes that interconnect with intracellular keratin filaments (Sherwood, 1997). A thin layer of cells containing granules of keratohyalin, the *Stratum grannulosum*, lies adjacent to this, and

is covered by a narrow layer of clear cells, the *Stratum cucidum*. The final, surface layer of the epidermis, the *Stratum Corneum* consists of flattened terminally differentiated keratinocytes (corneocytes) held within an intercellular lipid domain. This layer varies greatly in thickness at different body sites due to both genetic control of cell division and removal of dead surface cells by environmental conditions.

Figure 1.6 Schematic diagram of the epidermis
Showing differentiation of cells through different layers and approximate thickness of layers (from the commercial website of Eucerin Ltd)

1.6.2 Epidermal Lipids

Epidermal lipids play an important role in the differentiation, structure and function of the epidermis (Wertz & Downing, 1974). Lipid composition varies greatly as a function of differentiation of keratinocytes through the different layers (Kooyman, 1932) as the lamellar granules of the *Stratum spinosum* and *Stratum grannulosum* migrate toward the

periphery and form the lipids of the *Stratum corneum*.

Gray and co-workers showed the basal cells of the epidermis contained small amounts of cholesterol and a large amount of phospholipids. More mature granular cells contained higher concentrations of these lipid groups plus additional ceramides, glucoceramides and multilaminated sheets of free fatty acids (Gray, 1975). Long observed a gradual increase in cholesterol and free fatty acids from the basal layer to the *Stratum corneum*. Conversely, phospholipids were found to accumulate in the basal and granular cells but were completely degraded in the *Stratum corneum* (Long, 1975) and glucoceramides found in the viable layers of the epidermis are deglycosylated in the *Stratum corneum*.

Ceramides, cholesterol and free fatty acids thus constitute the major lipids of the *Stratum corneum*. Six structurally heterogeneous ceramides account for 50% of the total lipids found here. Cholesterol and cholesterol sulphate represent a further 25% and 5% respectively. Small amounts of cholesterol ester, cholesterol oleate and ester linked α-hydroxy acids are also present. Free fatty acids account for the remaining 10-15% of the lipids. These are mainly straight chain, saturated structures of between 14 and 28-carbons in length and along with cholesterol sulphate these are the only ionisable lipids in the *Stratum corneum*. The highly ordered rigid structure of the free fatty acids of the stratum corneum provides the principle barrier to the penetration of most compounds. Until 1904 when Schwenkenbecker demonstrated that skin was permeable to some lipophilic substances, the *Stratum corneum* was thought to be totally impermeable. It is now widely accepted that it is in fact semi-permeable; hydrophobic chains alternate with hydrophilic channels formed by the head groups of the lipids providing a polar route through the bi-layer.

Figure 1.7 Chemical structures of some skin lipids

(taken from the website of the Skin care Forum, www.scf-online.com)

The hydrophilic nature of viable epidermis underneath provides high permeability to polar molecules once they have passed across the *Stratum corneum*.

The skin surface is usually coated with a film of non-polar lipids (predominantly squalene), wax esters, triglycerides and free fatty acids, excreted from the sebaceous glands and subcutaneous fat (Wertz, 1974).

1.7 Polymeric drug delivery systems

1.7.1 Conventional drug administration

Conventional methods for drug/biological active administration, such as tablets and injections, require frequent and repeated doses and present problems in achieving and maintaining effective therapeutic drug plasma levels. Often an initial period of increased plasma levels, as the drug becomes available, is followed by a decrease in drug availability as the compound is metabolised, degraded or transported away from the treatment area (Langer & Peppas, 1981). This imposes the risk of toxic effects of high concentrations of the drug immediately after administration and is often followed by a drop of concentration below effective therapeutic levels by the time the next dose is due (Parthiban, 1997). (See figure 1.8 (a)) The problem can be exacerbated by poor patient compliance and, in the case of topical medicines, displacement of the carrier substance can result in insufficient treatment times. Attempts to minimise these risks through frequent administration of lower dosages of the drug often results in wastage of expensive drugs and inefficient treatment of conditions.

Figure 1.8 Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing
(Brannon-Peppas, 1997)

Many conventional systems, which include capsules, coated tablets and ointments, have been advanced to achieve sustained release of actives as a means of achieving some degree of control over these fluctuations. Although these systems prolong drug action/availability, measured release rates are often variable and subject to patient-to-patient variations and local environmental conditions. Additionally, multiple administrations are still required to complete a course of treatment. In order to fully exploit the therapeutic potential of a drug and to eliminate the risk of over- and under-dosing, it is desirable to maintain stable blood plasma levels within the effective concentration range shown in figure 1.8 (b). This can be achieved through the use of controlled release devices to deliver drugs and therapeutic agents.

1.7.2 Controlled release of drugs

In the 1950s research began into the incorporation of drugs into solid, natural and synthetic polymers from which the release of drugs could be engineered to suit the requirements of a specific application. Controlled release of a drug allows effective therapeutic levels of a drug to be administered over a prolonged period without the risk of over/under dosing and with reduced susceptibility to detrimental effects of poor patient compliance and environmental influence. Controlled release profiles can be constant over a long time period, cyclic over a long time period, or triggered by specific external or environmental changes, as specified by the design of the delivery device. Use of different polymer systems and drug incorporation procedures produces a wide range of release rates. It is often desirable that release is constant and follows a zero-order kinetic profile (release is independent of the amount of drug remaining within the delivery device) however usually only approximations to these criteria are achieved.

Drugs can be released from polymers via three main mechanisms, and any or all may exist within a particular system (Brannon-Peppas, 1997):

Diffusion of a drug through the polymer that forms the controlled release vehicle. This can take place either on a macroscopic level through the pores within the polymer matrix or on a molecular level, where the drug diffuses between the polymer chains.

Biodegradable devices breakdown within the body as a result of natural biological processes, releasing the drug at a rate dependent on both the rate of its diffusion through the polymer and the rate of dissolution of the polymer.

Swelling of initially dry polymers that are incapable of releasing a drug until bodily fluids are absorbed which increases the amount of aqueous solvent within the polymer and polymer mesh size, allowing **diffusion** of the drug out of the device.

Although controlled release devices avoid many of the problems associated with conventional drug administration methods, disadvantages do exist and these must be considered during the development of devices for specific applications. Langer & Peppas (1981) listed some of the potential advantages and disadvantages of controlled release technology, which are shown in table 1.2.

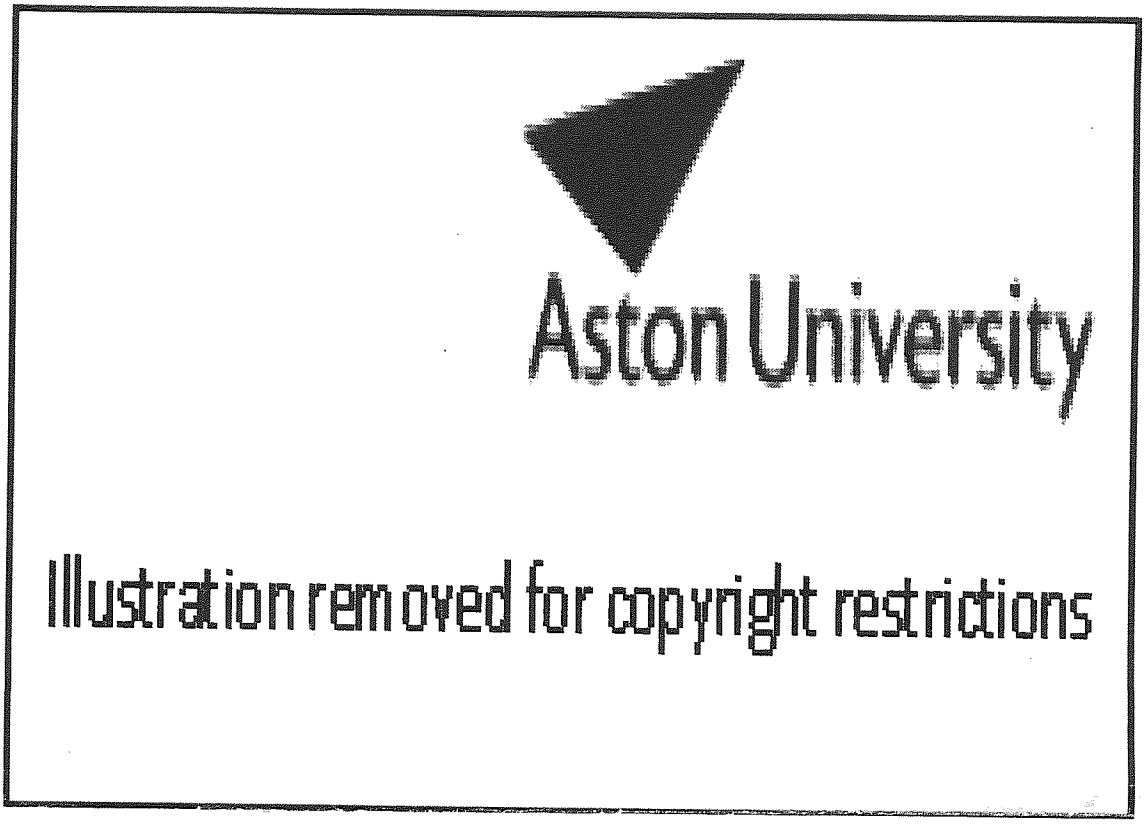


Table 1.2 Potential advantages and disadvantages of controlled release technology *(Langer & Peppas, 1981)*

A number of controlled release devices are in current commercial use and are summarised in several publications (Langer& Peppas, 1981, Gupta, 2002).

1.7.3 Diffusion-controlled devices

Studies within this research program concentrated on release of drugs and drug models from diffusion-controlled hydrogel devices wherein the drug simply diffuses through the polymer matrix into the external environment (figure 1.9). Permeation of a compound through a polymer is governed by thermodynamic and kinetic properties: the solubility of the compound in the material and its diffusion within the macromolecular matrix (Corkhill et al, 1990). As release from the polymer progresses, the release rate normally decreases as the distance to diffuse to reach the external environment increases. Indeed, many theoretical models propose that release rate is proportional to the inverse square root of time, i.e. first order. Membranes are often incorporated into matrix-diffusion devices to limit release into the external environment and maintain constant delivery rates.

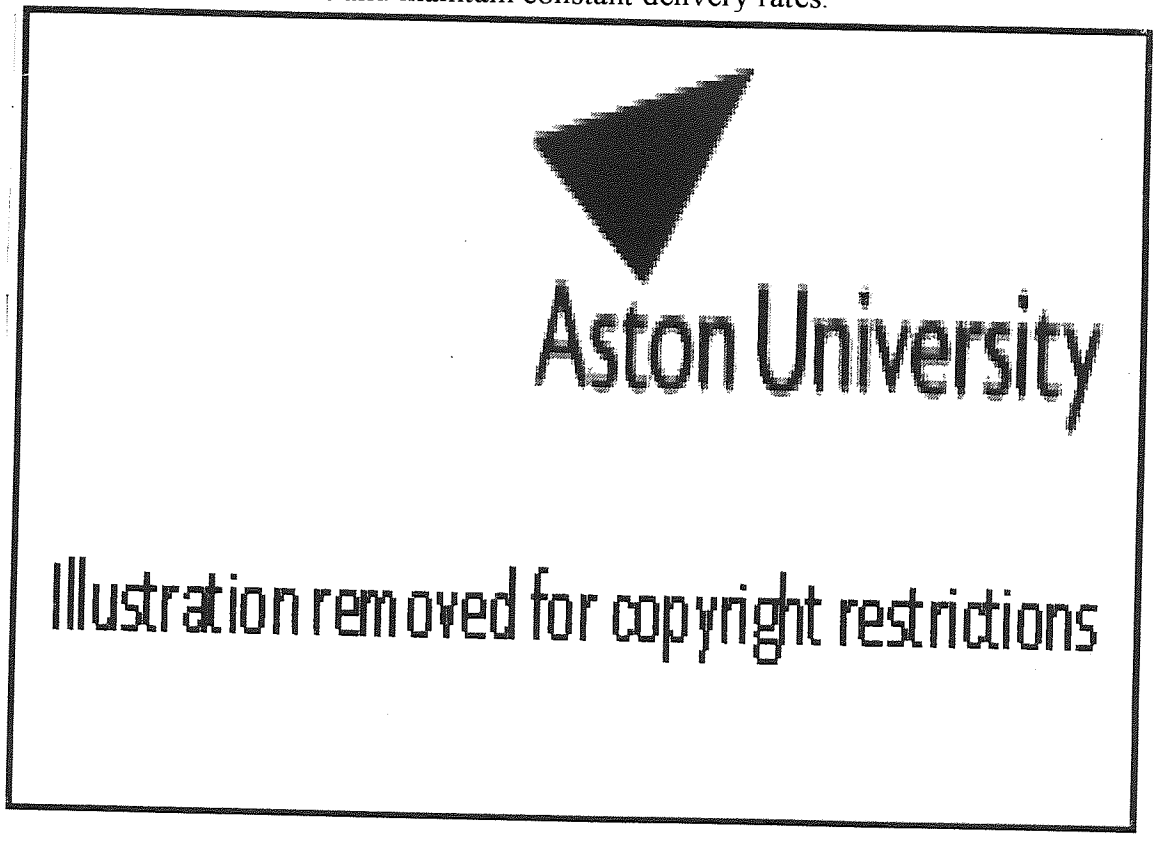


Figure 1.9 Drug delivery from a typical matrix-diffusion device
(Brannon-Peppas, 1997)

In their simplest form diffusion-controlled devices consist of a homogenous polymer membrane into which the drug, in either solution or particulate form, is incorporated,

supported by an impermeable backing sheet. In the case of matrix-diffusion devices for topical or transdermal drug delivery, such as those studied here, the polymer matrix may also incorporate the adhesive component of the device. Long-term compatibility between the adhesive and the loaded drug is important for the success of these devices. More complex variations on the matrix-diffusion device include multi-laminate systems made up of graduated layers of drug-loaded polymer to give more constant release rates (Lu & Anseth, 1999), and microporous systems in which the drug diffuses through liquid-filled pores within the polymer.

1.7.4 Incorporation of Active Compounds

The method of incorporation of active compounds within a matrix diffusion device is influential to its subsequent diffusion and release from the device. The compound can either be mixed with constituent monomer prior to polymerisation and subsequently trapped within the polymer matrix, or loaded into a pre-polymerised hydrogel by swelling the gel in a drug solution and drying to leave a drug impregnated material (Kim et al, 1992). Loading of pre-formed gels in this way has the advantage of avoiding any detrimental effects on the drug of polymerisation and purification of the hydrogel. Drugs and biologically active compounds can either be temporarily physically trapped within a hydrogel matrix or can be covalently bound to the polymer backbone depending on the chemical interaction of the compound with the polymer (Pedley, 1980).

1.7.5 Controlling diffusion and release

The design of a controlled release system is usually based on the physicochemical and pharmacokinetic properties of the loaded compound, polymer composition, changing conditions in the local environment and the interaction of all three. Polymer compositions can be manipulated to confer different rates of diffusion and release of a compound (Kim et al, 1992). Hydrophilicity of the constituent monomers of the

release vehicle, method of polymerisation, volume fraction of "free" water within the gel, pore size and distribution, and crosslink density all affect the permeation characteristics of the gel (Parthiban, 1997, Hoffman, 2002). Interactions of a loaded compound with the polymer, local environmental conditions, molecular weight, charge, and partition co-efficient of a drug will influence its solubility and diffusion through the hydrogel. Many theoretical models are available that can be used to estimate the effects of a range of factors on release profiles in order to aid the tailored design of systems (Iordanskii et al, 2000, Kalia & Guy, 2001). By manipulation of hydrogel characteristics it is possible to design polymers with release profiles for a particular drug that match the desired delivery configurations for a particular application (Griffith, 2000).

1.7.6 Transdermal drug delivery

Transdermal delivery of drugs provides an attractive means of administering medication systemically whilst bypassing hepatic first pass metabolism of the drug. It also allows rapid interruption of the treatment should this become necessary. Once a drug has been released into the external environment from a controlled release device it must go through a number of additional diffusional and active transport steps to penetrate the multi-layer barrier posed by skin. The mechanism of transport across the skin is not well understood but is made up of transcellular (across cells), intercellular (between cells) and transappendageal (shunt pathway) routes (figure 1.10). The transcellular pathway is the shortest route through the *Stratum corneum* and has the largest surface area, however, the density of corneocytes may present diffusional resistance to some drug molecules. The intercellular route, whilst avoiding diffusion through cell contents and so providing less diffusional resistance, occupies a much smaller surface area of the skin, limiting drug transport. Routes through the pores of appendages such as hair follicles and sweat ducts generally make up only a small proportion of the area available for percutaneous absorption, but can be utilised during iontophoretic delivery.

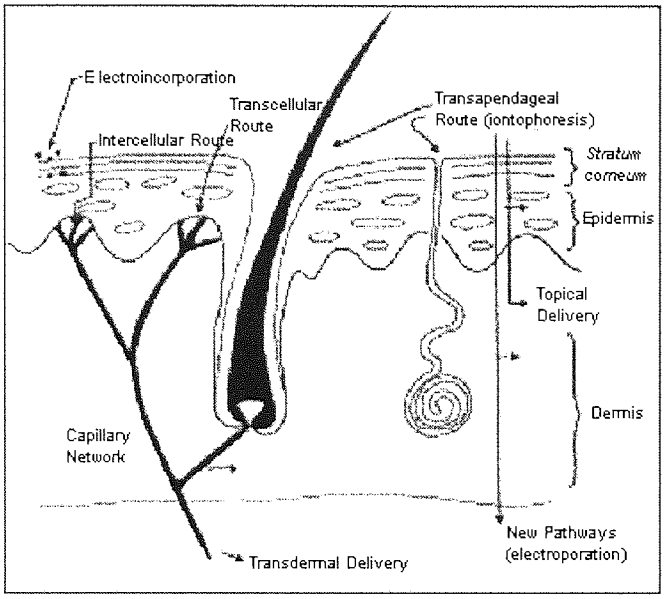


Figure 1.10 Showing the various routes for topical and transdermal delivery of drugs.

Development of transdermal drug delivery devices is limited by problems associated with skin penetration. During transport across the skin drugs can become trapped within the skin layers, creating a drug reservoir that leads to unpredictable release and diffusion kinetic of the drug. Additionally, barrier properties of the skin vary with age and location, influencing percutaneous absorption of the drug.

Transport of a compound across the skin may be passive or active. In the case of passive transport, diffusion occurs as a result of the concentration gradient across the skin and the differences in solubility of the compound in the skin and in the delivery vehicle (partition co-efficient). In many instances chemical penetration enhancers are also loaded into the device to be released with the active compound to aid its transport across the skin so that therapeutic plasma levels can be more readily achieved. A number of chemical agents have been accepted as being safe for use; these most probably act by modifying the physicochemical properties of the drug rather than indiscriminately impairing the barrier properties of the skin. Simple alkyl esters such as ethyl acetate have previously been used to give up to 650-fold increase in delivery depending on the agent. Active transport of a compound uses an external energy

source to assist drug transport across the skin. Heat, electric current (iontophoresis), soundwaves (sonophoresis), or transient high-voltage electrical pulses (electroporation) can be used (Tan & Pfister, 1999).

Chapter Two

Materials & Methods

2 Materials and Methods

2.1 Reagent Details

Details of all reagents used in this work are listed below in table 2.1. Structures for the materials are shown in section 2.2.

Reagent	Abbreviation	Molecular Weight	Supplier
2-Acrylamidoglycolic acid monohydrate	AMGA	163.13	Aldrich
Acrylic acid bis-(3-sulfopropyl)-ester, potassium	SPA	232.2	Rashig
Acryloylmorpholine 97%	AMO	141.17	Aldrich
L-ascorbic acid, 99%	Vitamin C	176.1	Aldrich
Benzophenone	–	182.22	Sigma-Aldrich
Benzil	–	210.23	Sigma-Aldrich
Bromopyrogallol Red	BPR	576.18	Aldrich
Butyl acrylate	Butyl A	128.2	Aldrich
Butyl methacrylate	Butyl MA	142.2	Aldrich
2,2-diethoxy acetophenone	–	208.25	Aldrich
Ebacryl II	Eb II	Confidential	U.C.B.

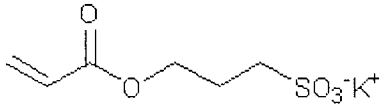
Reagent	Abbreviation	Molecular Weight	Supplier
Fluorescein	Fl	332.3	BDH
Fluorescein sodium salt	NaFl	376.3	Sigma
Glycerol	–	92.1	Fisons/Aldrich/ First Water
1-hydroxycyclohexyl phenyl ketone	Irgacure 184	204.3	Ciba
2-Hydroxyethyl methacrylate	HEMA	130.14	Cognis Performance
4-Isobutyl-alpha-methylphenyl-acetic acid 99%	Ibuprofen	206.3	Aldrich
Isopropyl myristate, 98%	IPM	270.5	Aldrich
Malachite Green Oxalate	MGO	927.03	Aldrich
α-methyl-4-[isobutyl]phenylacetic acid	Ibuprofen sodium salt	228.3	Sigma
Michler's ketone	–	268.35	Fluka
N, *N*-dimethylacrylamide 99%	NNDMA	99.13	Aldrich
N-methyl pyrrolidone	NMP	99.13	Fisher Chemicals
N-vinyl pyrrolidone	NVP	111.14	Vickers Laboratories
Oleylbis(2-hydroxyethyl)amine	Ethomeen OV/12		Akzo Nobel Surface Chemistry
Pentaerythritol tetraacrylate	PETTA	352	Aldrich

Reagent	Abbreviation	Molecular Weight	Supplier
Pentaerythritol triacrylate	PETA	298	Aldrich
pH 4 buffer (tablets)	PH4	–	Fisher Chemicals
Phosphate buffered saline (tablets)	PBS	–	Sigma
Potassium persulphate	–	270.32	Aldrich
Sodium 2-acrylamido 2,2 methylpropane sulphonic acid	NaAMPS	229	Lubrizol
Sodium metabisulphite, 97+%	–	190.1	Aldrich
Sodium persulphate, 98+%	–	238.1	Aldrich
Victoria Pure Blue BO	VPB	516.16	Aldrich
Vinyl butyrate	VB		Fluorochem Limited

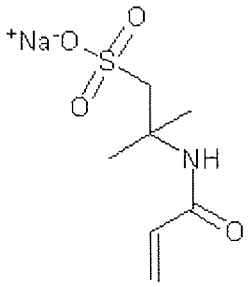
Table 2.1 Details of reagents used in this study.

2.2 Structures of Reagents

2.2.1 Structures of Monomers

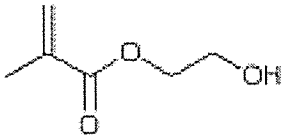


Acrylic acid bis-(3-sulphopropyl)-ester potassium salt (SPA)

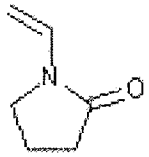


Sodium 2-acrylamido 2,2-methyl propane sulfonic acid (NaAMPS)

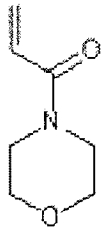
Figure 2.1 Structures of ionic monomers



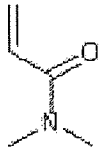
2-Hydroxyethyl methacrylate (HEMA)



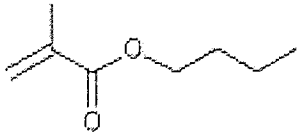
N-vinyl pyrrolidone (NVP)



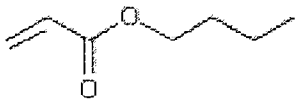
Acryloylmorpholine (AMO)



N,N-dimethylacrylamide (NNDMA)



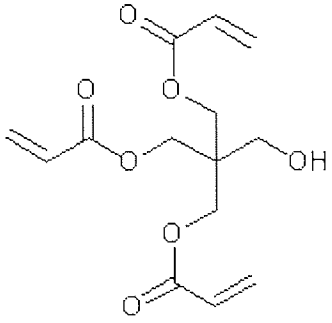
^{n}Butyl methacrylate



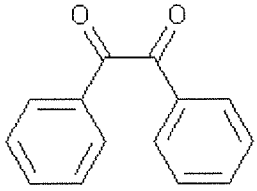
^{n}Butyl acrylate

Figure 2.2 Structures of neutral monomers

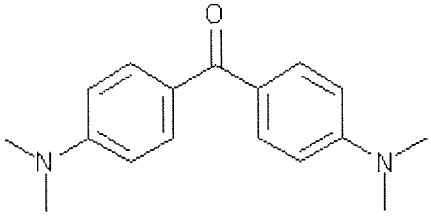
2.2.2 Structures of Photoinitiators and Crosslinking monomers



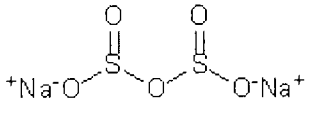
Pentaerythritol triacrylate (PETA)



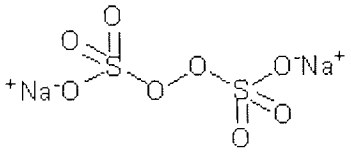
Benzil



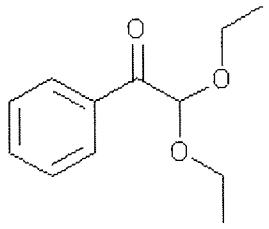
Michler's ketone



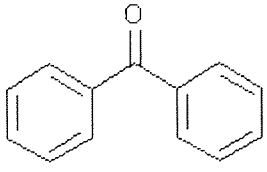
Sodium metabisulphite



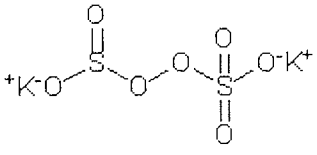
Sodium persulfate



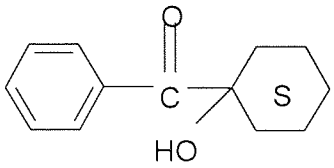
2,2-diethoxyacetophenone



Benzophenone



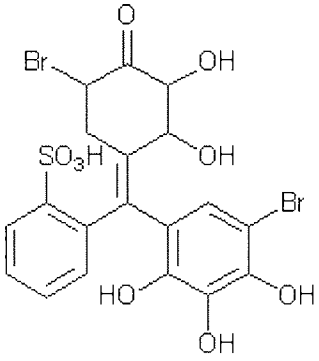
Potassium persulfate



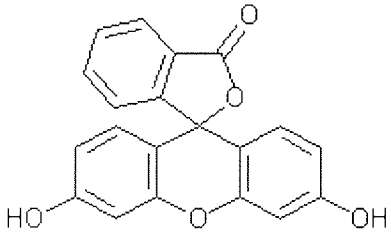
1-hydroxycyclohexyl phenyl ketone
(Irgacure 184)

Figure 2.3 Structures of photoinitiators and crosslinking monomers

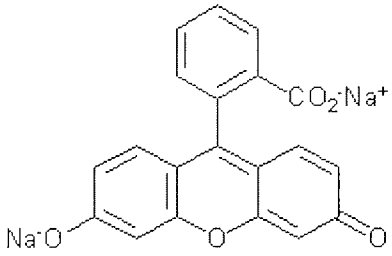
2.2.3 Structures of Release Compounds



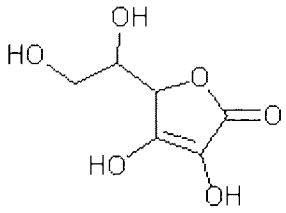
Bromopyrogallol red



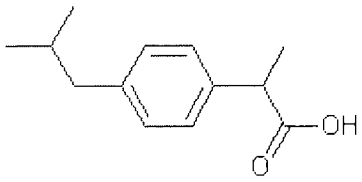
Fluorescein



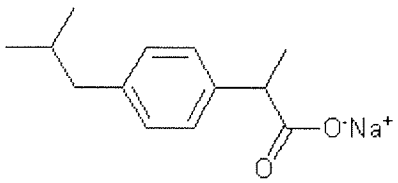
Fluorescein sodium salt



L-asorbic acid



4-Isobutyl-α–methylphenyl-
acetic acid



4-Isobutyl-α–methylphenyl-
acetic acid (sodium salt)

Figure 2.4 Structures of release compounds

2.3 Synthesis of hydrogels

2.3.1 Bulk and solvated samples for feasibility studies

Organic and solvated samples used in feasibility studies for the photopolymerisation of monomers within this laboratory were prepared and polymerised in small glass vials. Monomer(s), photoinitiator and crosslinking mixtures were prepared, as detailed in the results chapters of this thesis, and the open vials were placed under a static UV lamp (Gallenkemp, 125 Watts, wavelength unspecified). Samples were checked every five minutes for their state of polymerisation. Polymerisation times observed using this UV source were used as guidelines as to the relative degree of polymerisation of different hydrogel compositions.

2.3.2 Partially-hydrated membranes

Partially hydrated skin adhesive hydrogels were synthesised by photopolymerisation of monomer(s), distilled water and glycerol mixtures in the presence of small concentrations of photoinitiator and cross-linking monomer. Samples of 100g were spread on a release-paper lined tray and passed through a GEW ultraviolet lamp 310 at minimum belt speed until fully polymerised. After cooling the adhesive gels were covered with a sheet of release paper and stored in sealed plastic bags to prevent contamination and minimise water loss from the gel. Storage in this way has previously been shown (by First Water Ltd) to preserve the hydrogels for approximately six months.

2.4 Mechanical & physical characterisation

2.4.1 Rheology

Rheology is the study of the flow and deformation of matter. It describes the interrelation between force, material deformation and time. There are two components to deformation of a material; elastic and viscous. Elastic deformation of a material is accompanied by storage of energy within the material structure. When the deforming force is removed recovery of this energy allows partial recovery of the material to its original state. If the material is subjected to sufficiently high strain its structural properties will be destroyed and any further deformation will purely viscous. The viscosity of a material is a measure of its resistance to flow and is associated with a continuous input of viscous energy and permanent deformation of the material.

By using oscillatory flow characterisation techniques, which subject a material to a sinusoidally varying stress whilst never exceeding the strain which will destroy the elastic structure of the material, viscoelastic properties can be measured to give information on how a material is likely to behave under imposed shear stress conditions.

Shear stress is defined as the ratio of force applied and the area of the material to which it is applied (Equation 2.1). Shear strain is a measurement of the distance of material displacement divided by the height of the material sample (Equation 2.2). The rate of change of strain (shear rate) as a function of time is dependent on a material's viscosity (resistance to flow) (Equation 2.3).

$$Shear\ Stress = \frac{Force}{Area}\ Nm^{-2} \qquad \text{Equation 2.1}$$

$$Shear\ Strain = \frac{Displacement}{Height} \qquad \text{Equation 2.2}$$

$$Viscosity = \frac{Shear\ stress}{Shear\ rate}\ Nm^{-2}S\ (PaS) \qquad \text{Equation 2.3}$$

When a continuously changing stress is applied to a sample according to a sine wave equation ($y = \sin x$), a sinusoidally varying strain response will be induced. One complete cycle of the sine wave is taken as 360°. The differences of phase of the two waves (stress and strain) are known as phase angles. The strain response of a pure solid is directly related to and therefore will be in phase with the applied stress, giving a phase angle of 0°. The closer the phase angle is to 90° (the phase angle of a pure viscous liquid) the more fluid the behaviour of the sample.

Hooke's law relates strain to stress via the material constant, G (shear modulus).

$$Shear\ Modulus,\ G = \frac{stress}{strain}$$

At any one point during the oscillation test G relates to the ratio of stress amplitude to strain amplitude and is referred to as the complex modulus (G*). The complex modulus is the sum of the elastic component (storage modulus, G') and the viscous component (loss modulus, G")

$$G^* = G' + i \times G''$$

Values for G* and phase angles can be used together to define G' and G", giving values for elastic and viscous components of a material at a particular stress.

$$G' = G^* Cos\,\delta$$

$$G'' = G^* Sin\,\delta$$

Figure 2.5 Correct loading of parallel plate measuring system.
(Bohlin Instruments)

Viscoelastic properties of partially hydrated hydrogels were measured on a Bohlin CVO Rheometer using the oscillatory rheometrical technique. Samples were subjected to a sweep of 20 sine wave completion frequencies from 0.5Hz to 25Hz. Low frequency oscillation relates to long stress time scales such as those occurring when a skin adhesive hydrogel is applied to the skin. Higher frequencies represent the shorter stress times of gel removal. Samples of 20mm diameter were cut from hydrogel sheets using a size 13 cork borer and positioned in the centre of the base plate. The 20mm upper parallel plate was then lowered to the point of slight compression of the sample, ensuring good contact between the plates and the gel. This gap size varied with thickness of gel between 2.0 and 2.5mm. Correct loading of sample is important in order that measurements taken are from the area directly underneath the parallel plate only (see figure 2.5). To ensure uniform compression of the sample throughout the oscillation sweep a normal force control of 5% (100g) was specified. Tests were carried out at 37°C, normal body temperature, and repeated for each test material to verify reproducibility of data. Average values of at least three runs are quoted in the results. An ideal candidate material for skin adhesive applications should have tan δ values (ratio of viscous component to elastic component) of less than one. Higher tan δ values represent dominant viscous behaviour that is likely to result in cohesive failure of the gel upon removal. Good cohesive properties can be expected from gels with an elastic modulus (G') of between 10^3 and 10^5 Pa and a viscous modulus (G") of between 10^2 and $5x10^3$ Pa (First Water Hydrogels) A sample graph of oscillatory flow characterisation using this technique is shown in figure 2.6.

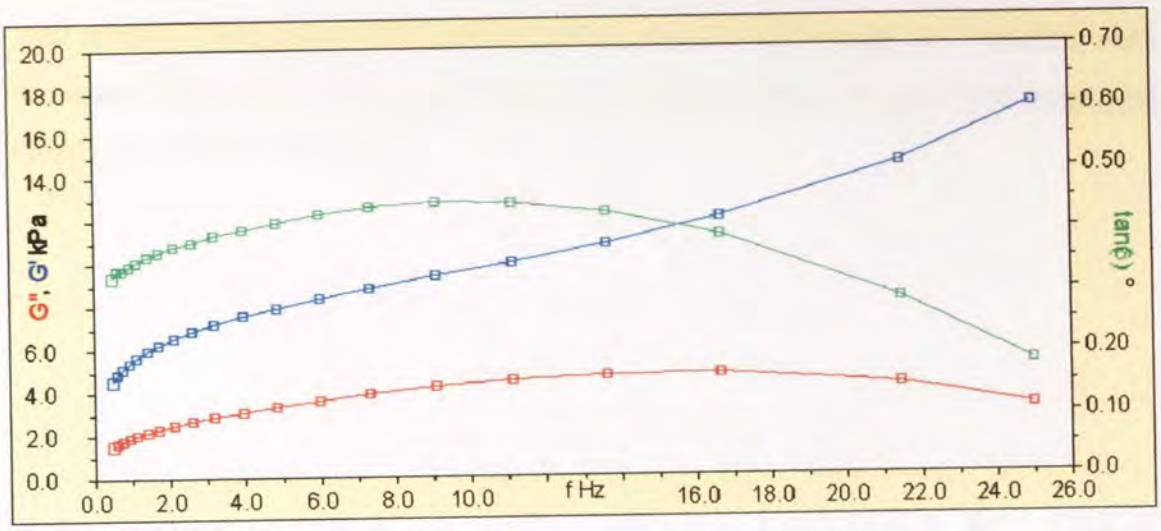


Figure 2.6 Sample graph of oscillatory flow characterisation

2.4.2 The 90 Degree Peel Test

The strength of an adhesive bond between a hydrogel and a substrate, in this case skin, can be measured using the 90° perpendicular peel test. This method measures the shear force required to induce adhesive failure at the interface between the hydrogel and the substrate. If adhesion here is sufficiently strong cohesive failure of the hydrogel will occur when a large force is applied.

The perpendicular peel test consists of two wooden platforms; a base support and a plate that slides over this base. The plate enables the subject's arm to slide over the base as the tape is peeled, allowing the angle of peel to remain constant at 90 degrees. This ensures the adhesive leaves the adherend directly below the peel grip. Strips of adhesive tape measuring 1.27cm x 12.7cm (½"x 5") were pressed against the subject's forearm. The strips were subsequently peeled from the skin by a grip positioned directly above the end of the adhesive at a speed of 500mm/min using a 100N load cell. Results of the peel were automatically related to a computer that determined values for peel strength in N/mm of the samples. At least three peel strength measurements were taken for each material tested, with a fresh gel sample used for each. Mean values of these measurements are quoted in the results. Ideally, peel strength values should be sufficient to ensure good adhesion of the gel to skin

with minimal discomfort upon removal. It is important to consider that variables such as contact area and pressure, application time, sample thickness, and peel angle and speed may influence results.

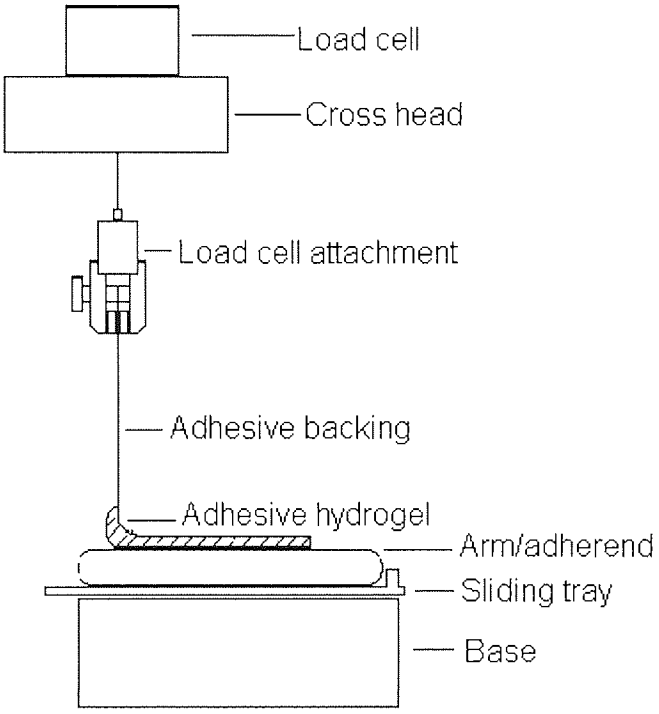


Figure 2.7 Diagrammatic Representation of the 90 Degree Peel Test
Adapted from a Hounsfield Hti tensometer, interfaced to an IBM 55SX computer with appropriate software

2.4.3 Critical point dryer

In preparation for Scanning Electron Microscope (S.E.M.) examination aqueous samples were dehydrated by critical point drying. This technique exploits the physical properties observed on the boundaries of a phase diagram. At a particular temperature and corresponding pressure on the boundary between liquid and vapour phases on a phase diagram, liquid and vapour exist together and have the same density. The water in hydrogel samples was replaced with an inert fluid, Freon (113). By raising the temperature of the sample to that at the point on a phase diagram where Freon can exist both as a liquid and vapour exist at the same pressure any liquid in the sample

can be changed to vapour without any change in density and accompanying surface tension effects on the morphology of the sample.

2.4.4 Scanning Electron Microscopy

Scanning electron microscopy is a non-invasive but destructive technique which allows the surface features of a sample to be viewed at very high magnifications. A stream of monochromatic electrons is directed at the sample as a thin beam. The electrons are collected as they are reflected off the gold sputter-coated surface of the sample and used to display an image onto a cathode ray tube. This thermal image of the sample is then recorded in the form of photographs.

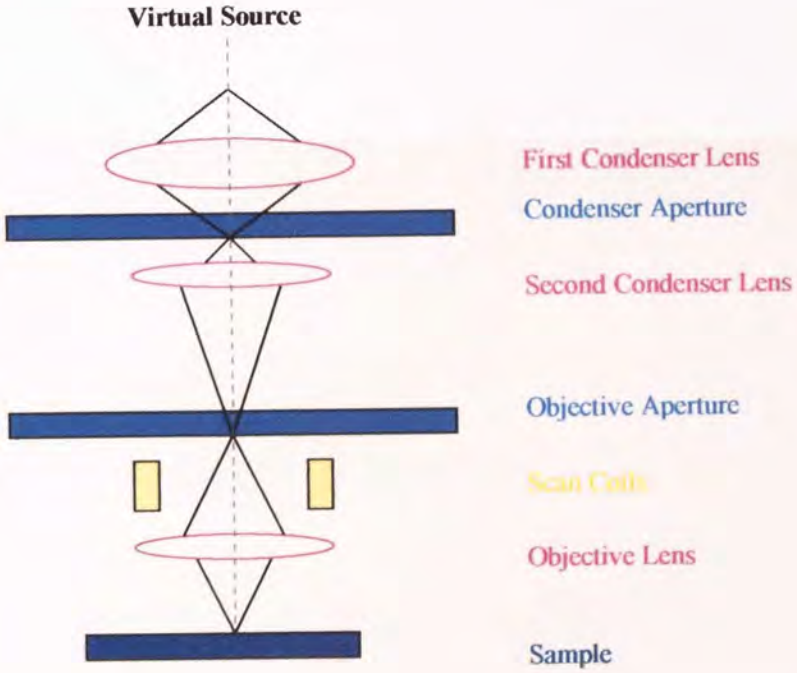


Figure 2.8 Schematic diagram of the projection of an electron beam onto a sample during S.E.M analysis

Strips of sample materials were applied to the subject's inner forearm and were removed either instantly or after a specified period of time (as specified in chapter 4) using the 90° peel method. In certain cases (quoted in results), subsequent peels of

fresh tape were performed at the same site as previous peels to allow examination of the effects of multiple application at a specific site. The application site was swabbed with alcohol between applications to remove any residual adhesive.

In the case of aqueous samples all water within the material was removed using a critical point dryer in preparation for S.E.M examination (section 2.4.3). Small sections of the samples (approximately $10mm^2$) were then placed application side up onto S.E.M. stubs and splutter coated with gold. The samples were examined using a Cambridge Stereoscan S.E.M. at magnifications of x100-250 at 25KV.

2.5 Analytical techniques

2.5.1 Colorimetry

Colorimetry involves shining light of a particular wavelength and intensity at a sample solution (incident light). By comparing the intensity of the incident light to the intensity of light transmitted through the sample, the absorbance (A) of the sample for that particular wavelength of light can be determined.

Analysis of the concentration of a coloured substance in a solution is based on Beer's law which relates the colour intensity of a solution (it's absorbance) to it's concentration (Equation 2.4).

$$-\log(I / I_0) = A = \varepsilon l c \qquad \text{Equation 2.4}$$

A = absorbance of sample
l = length the light travels through sample
c = sample concentration
I = transmitted intensity
I_0 = incident intensity
ε = extinction coefficient (substance- & wavelength-specific) (L mol^{-1} cm^{-1})

A series of solutions of known concentration were prepared for each release substance studied. Absorbencies of these were measured using the wavelength filter appropriate to each substance (quoted in results) with a Cecil CE404 colorimeter. The absorbance values were plotted against concentration to produce a calibration plot for each substance which was then used to determine from their measured absorbance the concentration of samples taken in release experiments.

2.5.2 Vertical diffusion cell

A Hanson 6-chamber vertical diffusion cell system was used to study *in-vitro* diffusion of loaded compounds from partially hydrated hydrogels across a membrane filter into receptor media. Each diffusion cell consists of an upper donor chamber separated from a lower receptor chamber by a membrane. A sampling port in the receptor chamber allows samples of release medium to be taken for analysis. A magnetic stirring system is used to prevent build up of a stagnant boundary layer adjacent to the release surface. This configuration was first popularised by Dr.T. Franz in 1978. Two sizes of diffusion cell (4.5ml and 7.0ml receptor chamber) were used in this work. A range of receptor media were used to study the combined effects of hydrogel composition, characteristics of loaded compounds, and receptor medium on release behaviour. In order to study the release of actives from the sample gels as opposed to transfer of the active across a membrane e.g. skin, a membrane was selected which did not present a significant rate-limiting barrier to diffusion of the active but acted as a scaffold for the hydrogels.

Hydrogel samples were cut using 9mm and 15mm cork borers to fit the dosage cavity of the 4.5ml and 7.0ml diffusion cells respectively. Release paper was left on the samples to aid their placement; samples were inverted so that the release paper did not form a barrier to release. Gelman Metricel membrane discs were used to support the hydrogel samples. This membrane was selected for its large pore size (0.45μm) which will not form a significant rate limiting barrier to loaded compounds. Pre-cut discs of the membrane were soaked in receptor medium for 30 minutes. Saturation of the membranes with the receptor medium fills the pores of the membrane, acting as a bridging agent for the release compound between the donor and receptor environments. This further reduces any rate-limiting effects of the membrane.

A saturated membrane disc was blotted with tissue paper on both sides to remove excess release medium and was centred on the Teflon dosage washer of the relevant diffusion cell. The dosage washer was then inverted and set on a paper towel ready for loading of sample. A hydrogel disc was then placed within the cavity of the dosage washer with the hydrogel in direct contact with the membrane. The receptor chambers of the diffusion cells were filled to slightly overflowing with the chosen receptor

medium. This reduces the possibility of formation of air bubbles between the release surface of the sample and the receptor medium.

The donor cell assembly was positioned on the diffusion cell with the membrane in contact with the release medium in the receptor chamber. It is advisable to "roll" the loaded washer onto the diffusion cell rather than simply place it on to avoid trapping air bubbles at the release surface. The donor cell was held in place with a top plate and secured with a clamp. A magnetic stirrer drive (Variomag Telemodul 40C electronic stirrer) provided an electromagnetic field to move magnetic stirring bars in the receptor vessels. Once samples had been loaded they were stirred continuously throughout the experiments at a speed of 200 r.p.m at 40% power.

Samples (300µl) of receptor medium were removed for analysis at regular intervals via the sampling port. These were immediately replaced with equal volumes of the relevant release medium to maintain contact between the receptor medium and the membrane.

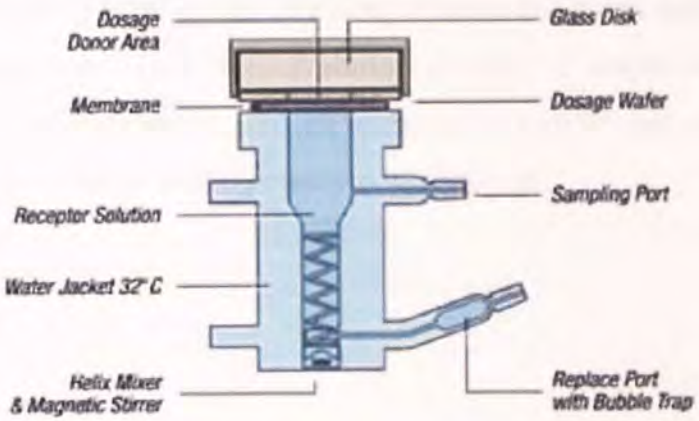


Figure 2.9 Schematic diagram of the Hanson vertical diffusion cell

2.5.3 High Performance Liquid Chromatography (H.P.L.C)

High performance Liquid Chromatography (H.P.L.C) is common analytical separation technique that can be used to quantify components of a chemical mixture. Samples of interest are injected into a solvent flow path (mobile phase) through an injector port and carried through a separation column (stationary phase). Differential non-covalent attractions between the components within the sample and the tightly packed beads in the separation column determine migration and separation of the sample allowing analysis and quantification of the sample components. Both column and mobile phase can be adjusted to manipulate interactions between the sample and the stationary phase.

Isocratic reverse phase HPLC of receptor media samples was used to quantify release concentrations. Reverse phase HPLC operates on the basis of the relative hydrophilicities of sample components. The hydrophobic stationary phase interacts with the components to differing degrees. More hydrophobic compounds, which interact more strongly with the beads in the column, are retained for longer than more hydrophilic components. Samples are eluted using a constant mobile phase composition in which all components of a sample begin migration simultaneously but migrate at different rates. This type of elution provides a simple and inexpensive method of sample analysis, which, through alteration of mobile and stationary phases and flow rate, allows a range of compounds to be analysed.

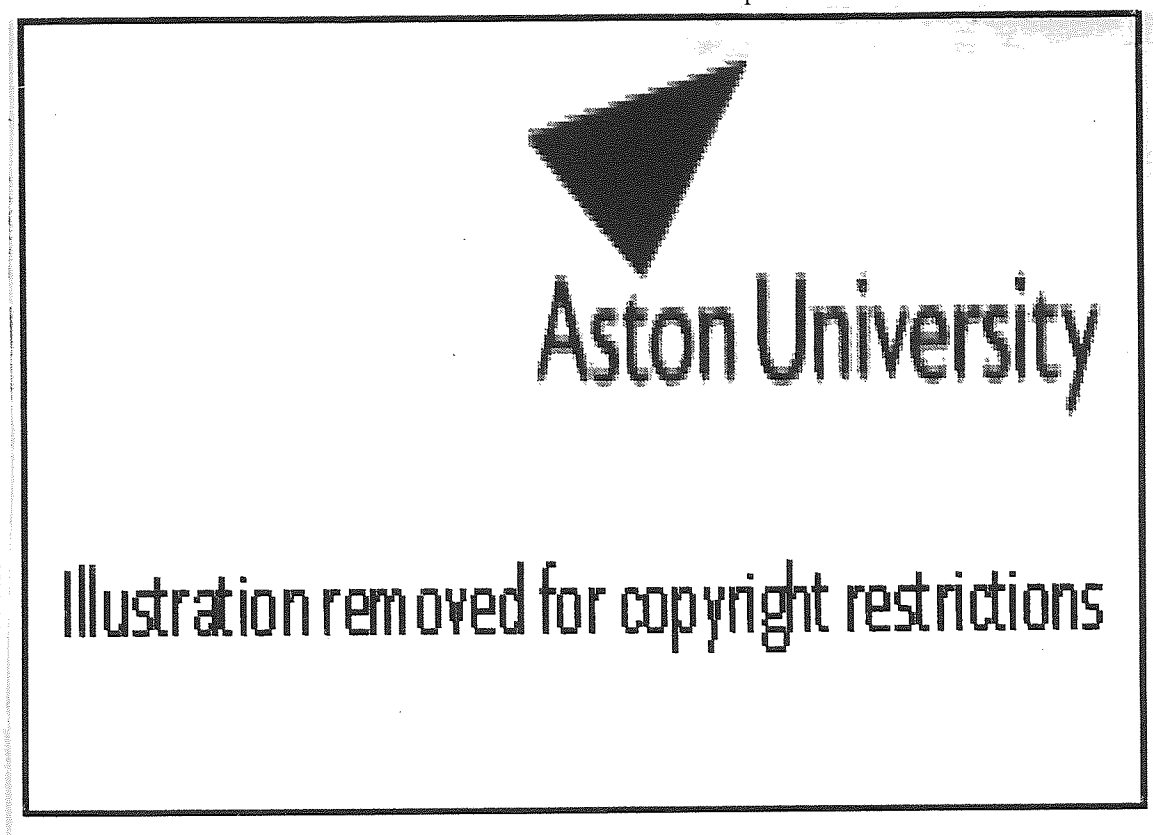


Figure 2.10 Block diagram of a high performance liquid
(Lindsay, 1987)

Compounds within a sample are identified by their elution time. Components of a sample can be quantified by use of internal or external concentration standards. In this work external standards were used. A series of known concentrations of the study compound were analysed under experimental conditions. The elution chromatogram for the standards gives a series of peaks, the area of which correlates to the concentration of the compound. Calibration curves can be generated for a compound and the polynomial equation of the curve used to find unknown concentrations of injected samples by relation to measured peak area.

Chapter Three

Photopolymerisation and Initiators

3 Photopolymerisation and Initiators

3.1 Introduction

Polymerisation of monomers to form gel network structures requires the presence of initiator and crosslinking agents, and the input of an energy source to initiate and crosslink the polymer chains. Interpenetrating networks (IPNs) (section 1.4.2), and semi-IPNs are formed in the same way but require the polymerisation to take place in the presence of a preformed crosslinked or (in the case of semi IPNs) linear polymer (see section 1.4.2).

Thermal energy is frequently used for polymerisation because of its versatility that allows both batch and continuous synthesis of polymers. However, this initiation technique requires relatively long periods of time and large production areas when used for sheet formation, making it unsuitable for the bulk production of large articles. Ultraviolet (UV) light is the preferred energy source for the polymerisation of large sheets of hydrogels, such as those used skin adhesive hydrogel production, as a clean, efficient and cost effective alternative to more traditional thermal cure methods. The reason for this is that the rapid initiation of polymerisation allows continuous coating and concurrent curing of long runs of polymer sheet which can be conveniently rolled and stored before further use.

Photopolymerisation involves the use of UV light in the visible spectral range (250-450nm) as an energy source. Photo-initiator agents absorb the UV light and undergo chemical change to form free radicals which are then used to initiate the formation of new chemical bonds by chain addition (Oster, 1990). The mechanism for initiation and propagation is shown in figure 1.3

3.2 Photoinitiators

The majority of the photoinitiators used commercially in free-radical chemistry are aromatic carbonyl compounds. On absorption of the appropriate wavelength of light an excited singlet state of the compound is produced which rapidly undergoes intersystem crossing to reach the lowest excited triplet state. It is from this state that actual photochemical reactions take place. Two major chemical deviation pathways are available to the triplet, depending on the substituents (figure 3.1). Type-I photoinitiators generate free radicals via unimolecular fragmentation (α-cleavage). Type-II photoinitiators undergo a bimolecular hydrogen abstraction, requiring the presence of a suitable hydrogen-donating source, such as a tert-amine, for the generation of free radicals (Hageman, 1991). Type-I photoinitiators are frequently chosen for commercial applications because of their high relative efficiency afforded by unimolecular fragmentation. All produce benzoyl (or substituted benzoyl) radicals which are very reactive towards the olefinic double bond of vinyl monomers. The other (unlike) radical produced simultaneously during primary fragmentation will either further contribute to the initiation process, undergo further thermal/photochemical fragmentation or participate in termination of the reaction, depending on its structure and the reaction conditions (Hageman, 1991). A range of α-cleavage photoinitiators are currently available (Ciba Additives) which provide the cure quality and speed demanded by the ever-expanding curing industry.

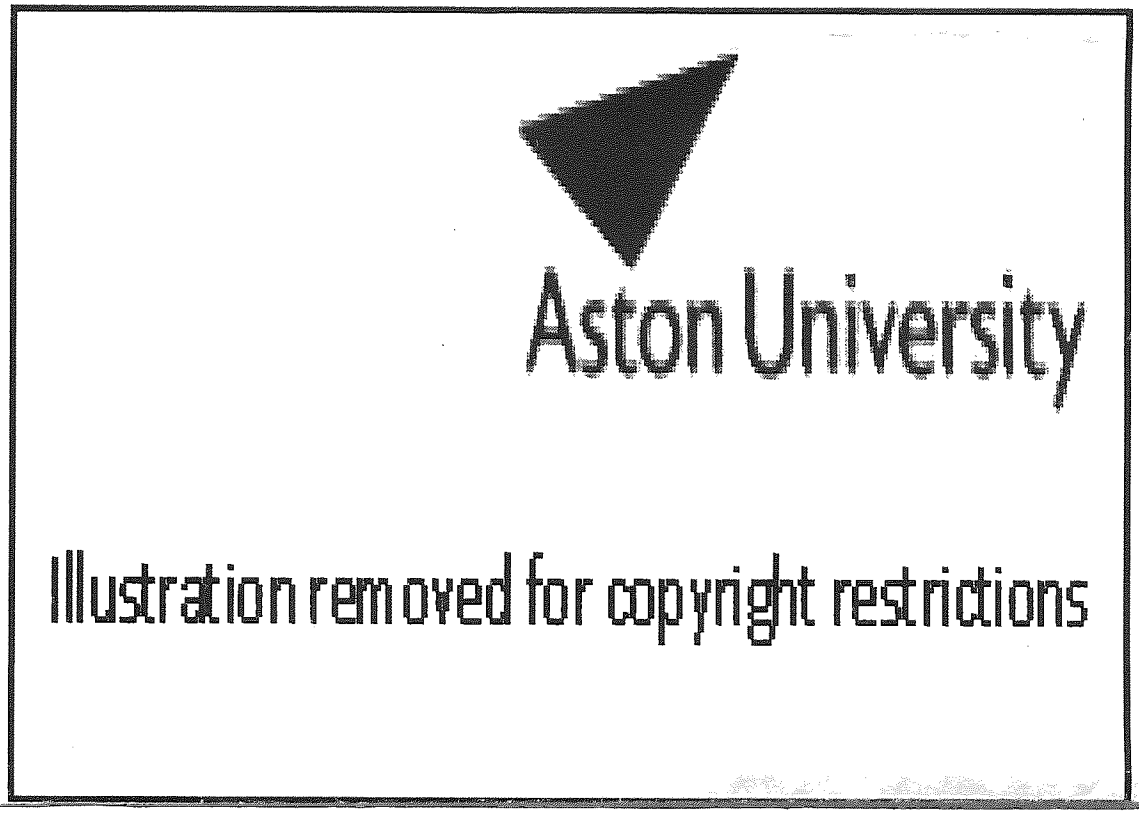


Figure 3.1 Type-I and type-II photo-initiation processes
(Hageman, 1991)

Irgacure 184 (a cyclohexyl phenyl ketone) and Daracure 1173 are now widely used in the commercial production of contact lenses and skin adhesives. The low sensitivity to air inhibition of Irgacure 184 is particularly suited to the relatively long exposure times required for polymerisation of these relatively thick samples. Irgacure 184 undergoes a Norrish type-I fragmentation when irradiated (figure 3.2).

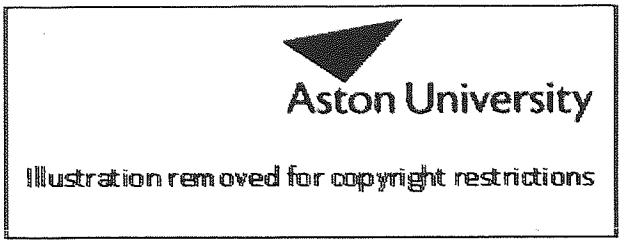


Figure 3.2 Schematic Norrish type-1 fragmentation of Irgacure 184 (Ciba additives)

Photopolymerisation of the monomers to form the gel network must be uniform to achieve consistent mechanical and adhesive characteristics throughout the gel. This relies on even production of reactive species to initiate polymerisation. Problems often occur in ensuring adequate and equivalent polymerisation of both the surface and the bulk of a hydrogel, particularly in the case of relatively thick samples as used here. Initiator decomposition and free radical formation is greatest at the surface of the gel due to greater light intensity. As optical density increases through the deeper layers of the gel, cure of the lower layers of the gel is hindered by reduced free radical production.

A significant problem encountered during the photopolymerisation of samples with a large surface area (hydrogel sheets) is oxygen inhibition of complete polymerisation at the hydrogel surface. The presence of oxygen species in the atmosphere at the sample surface can reduce the number of reactive species available for polymerisation by either quenching the excited triplet state of the photoinitiator or reacting with the primary initiating radicals itself (figure 3.3). In some cases oxygen-inhibition may be eliminated by polymerising the gel in either a vacuum or in the presence of an inert gas. However, in the case of skin adhesive hydrogel sheets, the large increase in production costs and impracticalities of producing the gels in this way make this technique unsuitable.

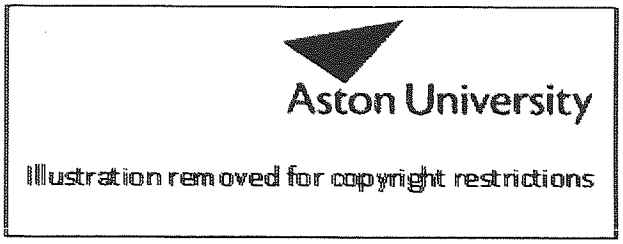


Figure 3.3 The fragmentation and quenching processes involved in oxygen inhibition *(Salim, 1991)*

An alternative method of oxygen-depletion is the use of higher concentrations of photo-initiator to provide increased concentrations of primary radicals or the use of readily oxidised trapping agents, such as tert-amines, to "mop-up" oxygen (Salim, 1991). Although increasing photo-initiator concentration provides a potential solution to the problem of incomplete surface cure, the accompanying increase in optical density of the gel reduces light absorbance in the lower layers of the gel and can result in non-uniform polymerisation of the gel, as described previously. Use of excessive radiation can result in yellowing and embrittlement of the polymer. Care must be taken to find a balance between these two extremes if a good quality hydrogel is to be produced.

3.3 Monomers

A range of monomers were studied to establish which might provide alternatives to NaAMPS in the production of skin adhesive hydrogel systems. Current patent holdings and applications (US 2002/0026005, WO 03/077964, WO 03/097116) impede the development of novel commercial devices using this monomer, and limitations of the monomer itself leave room for the development of new, more effective systems. Table 3.1 below lists the monomers studied and indicates some of their specific properties which have been influential in their being chosen as a potential means of expanding the range of applications for which skin adhesive hydrogels can be specifically tailored.

Monomer	Properties
N,N-Dimethylacrylamide (NNDMA)	Good water solubility Frequently used in biomedical hydrogel synthesis
Acryloylmorpholine (AMO)	Hydrophilic nitrogen-carbonile group Mildly electron donating monomer Good water solubility
Hydroxyethyl methacrylate (HEMA)	Hydrophilic Stable under varying physiological conditions
N- Vinylpyrrolidone (NVP)	Heterocyclic High polarity High thermal and hydrolytic stability Mildly electron donating monomer Good water solubility
Butyl acrylate	Challenge monomer
Butyl methacrylate	Steric hindrance by ∝-methyl group; challenge monomer
Vinyl butyrate	Challenge monomer

Table 3.1 Monomers studied and their properties

3.4 Aims of chapter

Although rates of polymerisation and co-polymerisation in organic media have been intensively studied and the individual reaction steps in the polymerisation (schematically represented in figure 1.4) evaluated for many combinations of monomers, initiators and solvents, polymerisation in concentrated aqueous media has not been widely examined. Rules of thumb might be expressed as follows:

- Hydrophilic monomers are preferable to hydrophobic monomers because of the compatibility issues involved in the development of skin adhesive hydrogels.
- Methacrylates polymerise more slowly than acrylates because of the steric effects of the α-methyl group.
- Acrylamide and its derivatives polymerise more rapidly than acrylic acid and its derivatives.

This thesis is concerned with the practical use of monomers in the formation of adhesive hydrogels for practical skin contact applications rather than the detailed study of rates of reaction of individual monomers. For this reason, empirical comparative studies on relative suitabilities of monomers were carried out, rather than kinetic studies of rates of polymerisation, under controlled and systematically varied conditions. Details of reaction kinetics of monomers can be found in a number of standard texts such as Bamford et al (1960).

Rather than seeking to systematically improve skin adhesive properties, the purpose of this chapter was to examine briefly the potential of other hydrophilic monomers for incorporation into skin adhesive gels in order to increase scope for influencing such properties as, for example, controlled release characteristics. Work involved optimisation of the photopolymerisation of monomers in aqueous media to form adhesive hydrogels to support subsequent functional research. A range of monomers was investigated for their relative ease of polymerisation under these laboratory conditions with the aim of broadening the portfolio of monomers available for use in the production of skin adhesive hydrogels.

3.5 Procedures

All photopolymerisation samples were prepared using a standard technique. Each sample consisted of bulk monomer (2g) and a standard concentration (w/w) (0.13%, 0.0026g) of UV initiator/crosslinker mix. This mix consisted of a 10:3 ratio of Ebacryl (acrylic crosslinker) and Irgacure 184. A new batch of this mixture was made-up every 7-10 days to ensure its effectiveness.

The standard crosslinker and initiator, plus any additional initiator required for specific experiments, as described later, were weighed into glass sample vials on a Mettler AE240 analytical balance. The bulk monomer, and in certain cases solvent, were then added. Actual weights measured were recorded.

Bottle lids were replaced and the bottles wrapped to block out daylight and prevent premature photopolymerisation. The samples were then placed on a shaker to ensure homogenous distribution of the initiator mixture. For the majority of samples the solid components of the samples were readily dissolved in the liquid components to produce a homogenous sample, although in a few exceptions, indicated in experimental descriptions in this report, undissolved precipitate remained in the sample even after additional shaking.

The lids of the sample bottles were removed and the bottles were placed under a Gallenkamp ultra violet lamp of 125 Watts and unspecified wavelength. Samples were polymerised in the bottles as thick layers rather than as sheets, such as those produced in industry, as comparative data as opposed to specific polymerisation times for different monomer/initiator systems were required. Sample depths for individual experiments are detailed within specific experiment descriptions. The monomer solutions were observed every 5 minutes and taken from underneath the UV lamp when they appeared either to have completely polymerised to form glassy polymers or had remained at an apparent constant viscosity for sufficient time for it to be assumed that maximum polymerisation for such a composition was complete. Times to reach such stages were noted and the appearance of the samples described.

3.6 Results

3.6.1 Current commercial system, Irgacure 184, in organic and aqueous systems

Irgacure 184 is among the current choice of photoinitiators for the commercial production of hydrogel sheets such as those used in the manufacture of medical hydrogel adhesives. As such it provides a good basis for preliminary investigations into the photopolymerisation of monomers to produce skin adhesive hydrogels within this laboratory. Currently, a limited range of hydrophilic monomers is used in the commercial production of skin adhesive hydrogels. As a starting point for broadening this range Irgacure 184 was used to establish the potential of a number of monomers for photopolymerisation within this laboratory.

Relative polymerisation times and resultant polymers of bulk and solvated systems of seven monomers were studied. Polymerisations were carried out using bulk organic samples (thickness = 5mm) and at two monomer to solvent ratios; 5:1 monomer to solvent (thickness = 8mm) and 1:4 monomer to solvent (thickness = 25mm). These allowed the effects of both the presence and the volume fraction of solvent on extent of polymerisation and time to complete polymerisation to be studied and compared for the different monomers. Water was used as solvent for those monomers which are water-soluble (NVP, NNDMA, AMO) and N-methyl pyrrolidone (NMP), a water-miscible organic diluent, was used as an alternative for those which were not (HEMA, VB, Butyl MA, Butyl A).

Samples were prepared as described previously, with standard 0.13% (w/w) Ebacryl II and Irgacure 184 crosslinker/initiator (10:3) mix, plus an additional 0.25% (w/w) Irgacure 184 (photoinitiator) to ensure that initiator concentration was not a limiting factor in polymerisation of the samples. The samples were photopolymerised in unsealed glass vials as detailed in 2.3.1 and their relative polymerisation times were observed and resultant polymers described. Complete polymerisation was judged to have occurred when the polymer behaved as a solid i.e. didn't flow when the sample bottles were inverted.

Photopolymerisation of bulk monomers resulted in the rapid production of clear glassy polymers from samples of NNDMA, AMO, HEMA and NVP. Polymerisation times of these monomers, though not ideal, indicate the potential of the monomers in photopolymerisation applications. Butyl methacrylate also formed a clear glassy polymer but this required over 100 minutes exposure to the UV source, an excessive time for practical use of the monomer under these experimental conditions. Neither butyl acrylate nor vinyl butyrate polymerised fully during the 135 minutes of experimental time.

Clear glassy polymers were also produced from many of the monomers in low ratio (5:1, monomer:solvent) solvated systems. Polymerisation times were longer for some of the monomers when compared to the organic bulk system but increased sample thickness should be taken into consideration as a possible reason for this. As before, butyl A and VB did not polymerise fully; an increase in the viscosity of the butyl A sample was observed and VB remained as a clear liquid.

An increase in solvent content of samples to 1:4, monomer:solvent was detrimental to the polymerisation times of most of the samples, with the exception of NNDMA and AMO, which polymerised fully to form solid hydrogels within 10 minutes. It should be noted that some residual liquid remained in these samples but it is thought that this may have been excess solution remaining after consumption of all of the photoinitiator. HEMA at a 1:4 dilution polymerised slowly (180 minutes). After 190 minutes all other samples remained as clear liquids with no visible signs of polymerisation with the exception of an increase in the viscosity of the NVP sample. Lack of polymerisation at the sample surface however, suggests that the sample composition itself was key to the failed polymerisation.

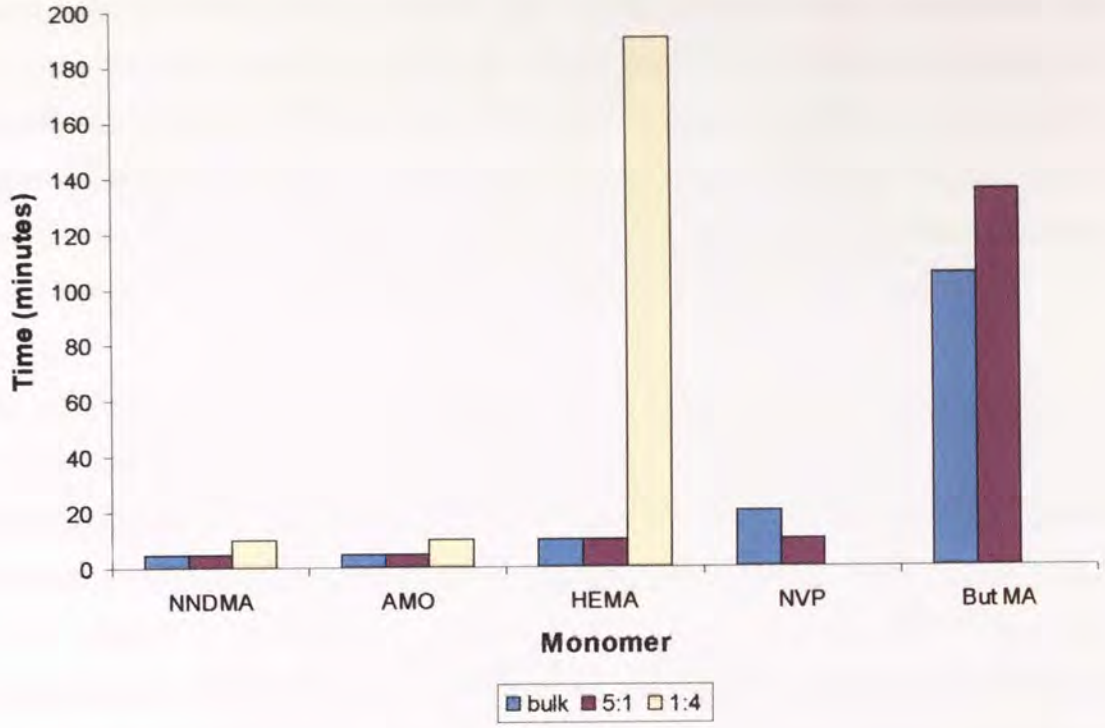


Figure 3.4 Effect of solvent on polymerisation
Polymerisation times of organic and solvated samples with a current commercial photoinitiator system, Irgacure 184 (5 minute error bars shown)

Those monomers with more hydrophilic tendencies polymerised more rapidly than those monomers with greater hydrophobic tendencies. The structures of the more hydrophilic monomers; NNDMA, AMO and HEMA, promote the addition and propagation of a free radical, which in turn propagates polymerisation. The relatively short observed polymerisation times of NNDMA, AMO, HEMA and NVP indicate the potential for use of these monomers in skin adhesive hydrogels. Subsequent experiments using alternative initiator/crosslinker systems will be used to investigate the possibility of further reducing these times.

Several of the monomers studied demonstrated impractically long polymerisation times or failure to polymerise fully. The relatively long polymerisation times of Butyl MA and Butyl A and the failure of VB to polymerise completely within a practically useful time indicate that these monomers may not be suitable for use in commercial applications. These monomers may have lower susceptibility to the utilisation of free radicals for polymerisation. It should be noted that when taking the chemical structures of these monomers into consideration, that of Butyl A should facilitate

faster polymerisation of the monomer than of Butyl MA. In these experiments this was not the case, and the presence and potential of variation in potency of manufacturer-added inhibitors in the monomers must be considered. The excessive times to complete polymerisation that were observed this experiment suggest that the absence of such inhibitors would, however, be unlikely to make sufficient differences to the polymerisation times to render the monomers commercially viable.

The effect of solvent on polymerisation of the monomers appears to be dependent on solvent concentration and monomer structure. The presence of solvent at the lower concentration of 5:1 appears not to be detrimental to either degree of polymerisation achieved or time until polymerisation is reached (for NNDMA, AMO, HEMA, and NVP). Indeed, a previously undocumented phenomenon was observed in the polymerisation of NVP in aqueous solution. The presence of water at this ratio halved the time taken to achieve the same degree of polymerisation observed in the absence of solvent. The aqueous environment appears to have facilitated an increased reactivity ratio of the monomer structure with the initiator/crosslinker system. Such results are promising in terms of use of solvent both to aid faster polymerisation of selected monomers and to act as a plasticizer within hydrogels to be used as skin adhesives. Potential subjectivity when visually judging times to complete polymerisation in these experiments must, however, be taken into account and the possibility of undetected incomplete polymerisation considered.

Results of these experiments highlighted the detrimental effects of the presence of solvent at higher ratios such as 1:4. All seven monomer samples contained residual liquid after removal from the UV source. Although very low viscosity gels would be expected of such high solvent content samples, the presence of liquid in samples which had (under different conditions), polymerised rapidly and completely, suggests the liquid to be excess monomer/solvent solution for which there was insufficient initiator/crosslinker mix to effect polymerisation. The increased thickness of these samples is likely to have been a factor in hindrance of polymerisation, with optical density within the gel increasing and blocking UV initiation in the deeper layers of the gels. The failure in the presence of solvent at either of the concentrations used to facilitate polymerisation of VB or Butyl A further indicates their lack of suitability for use in skin adhesive hydrogels.

3.6.2 Optimum concentration of Irgacure 184 in organic and aqueous systems.

In order to be of developmental use within this laboratory, and eventually commercial use, it is essential that any monomers used in novel systems can be rapidly polymerised with minimal residuals. As mentioned in section 3.2, one method of increasing the number of primary radicals available for polymerisation is to use increased concentrations of photoinitiator. Levels must be moderated to avoid detrimental increases in optical density and greatly reduced backbone chain length caused by low monomer:initiator ratio. A ladder study of a range of concentrations of Irgacure 184 was used to establish optimum photoinitiator levels for hydrogel production in this laboratory using those monomers which previously showed potential as a means of increasing the range of monomers available for the production of new skin adhesive hydrogel materials. Figures 3.5 and 3.6 show the polymerisation times for organic and aqueous monomer systems respectively, in the presence of increasing concentrations of photoinitiator in addition to the standard 0.13% (w/w) as used in section 3.6.1.

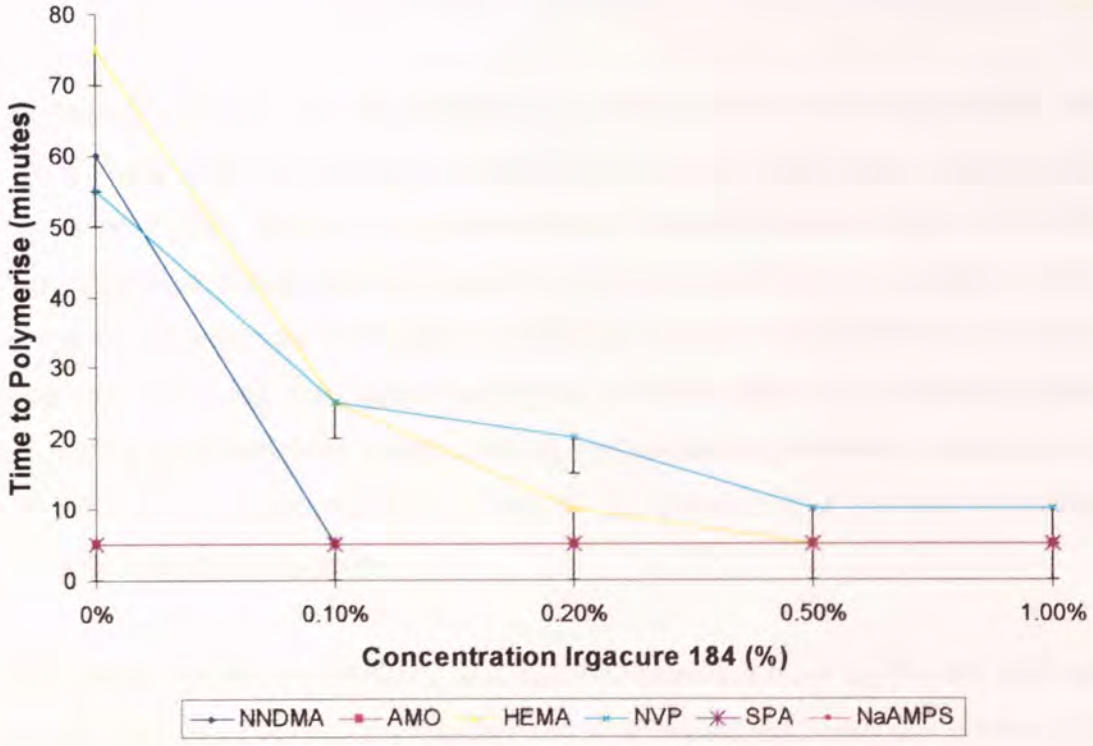


Figure 3.5 Effect of increasing concentration of Irgacure 184 in organic systems
Polymerisation times of organic systems with increasing concentrations of additional Irgacure 184 (5 minute error bars are shown)

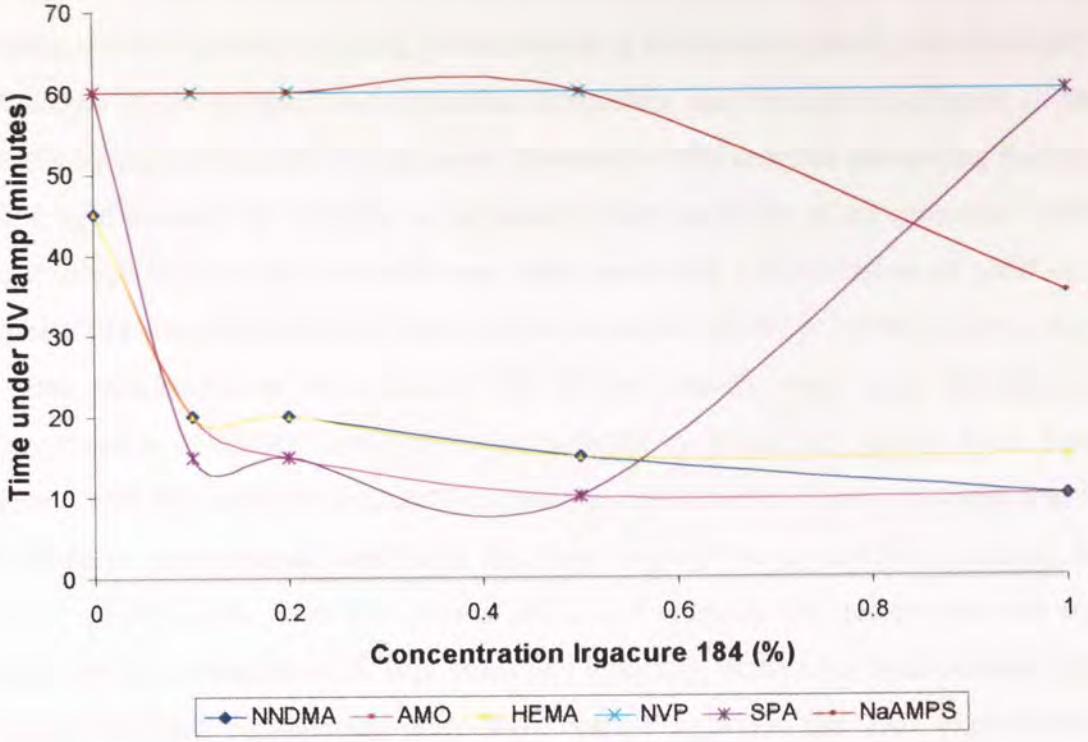


Figure 3.6 Effect of increasing concentration of Irgacure 184 in aqueous systems
Polymerisation times of high ratio aqueous systems with increasing concentrations of additional Irgacure 184. (5 minute error bars are shown)

The organic systems for both HEMA and NVP polymerised most rapidly with concentrations of 0.5% additional Irgacure 184 to form clear glassy polymers and showed no further decrease in polymerisation time with concentrations above this level. Minimum polymerisation times for NNDMA and AMO in organic systems were achieved with only 0.1% and no additional Irgacure 184 respectively, with both monomers producing clear glassy polymers. Bubbles within the polymers indicated that boiling point had been reached during polymerisation, directing attention to the possibility of use of combinations of thermal and photo initiator systems to facilitate more efficient polymerisation.

The aqueous systems for NNDMA and AMO polymerised most rapidly and with least residuals with an additional 1% Irgacure 184. Concentrations below this produced low viscosity gels and significant amounts of residual liquid. Residuals were a greater problem in the case of the aqueous HEMA system, even at concentrations of 1% additional Irgacure 184. Gels produced were white and opaque suggesting phase

separation. None of the samples of NVP polymerised completely, but viscosity of the samples increased with increasing concentration of additional Irgacure 184. It is likely that failure of the samples to polymerise completely was because of dilution of the initiator by the solvent and the increased thickness of the samples preventing passage of UV light through the samples, as opposed to poor reactivity of the monomer itself. The increase in viscosity that was seen with increasing concentration of additional Irgacure 184 suggests the possibility that the monomer would polymerise completely at these concentrations of Irgacure 184 if less solvent was used. Results for polymerisation of HEMA and NVP in an aqueous system differ greatly from those obtained with the same system used in previous experiments. This is possibly due to variations in experimental conditions that were beyond the researcher's control. As the two experiments were not carried out simultaneously but rather over several weeks, laboratory temperature, brightness and humidity, ultraviolet light intensity and monomer/initiator composition may have varied between the two experiments, affecting the results obtained. The purpose of this study was, however, primarily to determine relative polymerisation times of the monomers with different initiator systems, and the effects of varying concentrations of specific systems on each monomer. As such, comparisons are qualitative rather than quantitative and within individual experiments as opposed to between the different experiments. Therefore, the differences seen do not affect the information taken from the study here, but highlight the interesting importance of environmental factors on polymerisation time.

The polymerisation times of all of the monomers were increased in the presence of solvent, and, in the majority of cases, optimum concentration of additional Irgacure was higher in the presence of solvent and did not decrease polymerisation time as greatly as in the absence of solvent.

3.6.3 Alternative industrial photo-initiator systems

Although Irgacure 184 and other α-cleavage photoinitiators from the same range (Ciba Additives) are successfully used in the commercial production of medical hydrogels. The potential of photoinitiator combinations used in other areas of the

curing industry was considered as a means of solving the problem of toxic residuals, a significant and obvious limitation in the development of novel hydrogels for biomedical applications. Two systems were studied, both of which are used in the curing of polymer coatings for food can linings. Compositions of each system are shown in table 3.2.

System A	Benzophenone	5.00g
	Michler's ketone	2.00g
	Benzil	3.00g
System B	Benzophenone	2.50g
	Michler's ketone	0.15g
	Diethoxy acetophenone	0.75g

Table 3.2 Compositions of two industrial photoinitiator systems

As both systems included components in solid form, crushed and uncrushed samples were prepared. Organic and high ratio (1:4) aqueous systems of NVP, NNDMA, VB and Butyl MA were studied.

System A

Both organic and aqueous systems of all four of the monomers failed to polymerise or increase in viscosity after 65 minutes under the UV lamp in the presence of either crushed and uncrushed photoinitiator mix, and in the presence and absence of solvent. It is speculated that this initiator mix was used at too low a concentration to be effective. Increasing the concentration used to that suggested by its users in industry would however be unsuitable for hydrogels for medical applications considering the likely resultant high levels of residuals.

System B

For all four of the monomers with which this system was used, the mix failed to dissolve whether crushed with a pestle and mortar, or left uncrushed, and in the presence and absence of solvent. In the uncrushed state the mix remained as flakes suspended in the monomer solution and when crushed and added to the monomer, a

blue paste was formed. It is also noted that the strong colouring of the initiator mix may have been a problem in terms of aesthetic properties of gels.

3.6.4 Combination of thermal initiator (potassium persulphate) with Irgacure 184

Although photopolymerisation utilises UV light energy during polymerisation, a small amount of heat energy is also generated by the UV source and the exothermic polymerisation reaction.. Usually this additional energy is wasted as it cannot be used by photoinitiators to produce free radicals.

In addition to the standard 0.13% Irgacure and Ebacryl mix a thermal initiator, potassium persulphate, was added to monomer samples in place of the additional Irgacure 184 used previously, to determine whether thermal energy could be used to aid the polymerisation.

$$S_2O_8^{2-} \xrightarrow{heat} SO_4^{-}\bullet \qquad \text{Equation 3.1}$$

Both bulk and 1:4 monomer to solvent ratio samples were prepared and polymerised by the standard method. For simplicity, these initial reactions using waste heat energy were carried out using potassium persulphate alone, but it should be noted that potassium persulphate can also be conveniently used with redox "accelerators" such as thiosulphate or sulphate in the form of metabisulphite. When used in this way an opportunity is presented to use the molecular oxygen, present at increasing concentrations towards the surface of an exposed film, in the polymerisation process. Due to the failure of Butyl A to polymerise, either in the presence or absence of solvent, the monomer was removed from the study at this stage as it was considered to be unsuitable as an alternative monomer for use in hydrogel preparation. VB and Butyl MA remained in the study as it was hoped that use of an alternative initiator

system might prove successful for these monomers. Figure 3.7 below shows polymerisation profiles for the organic systems.

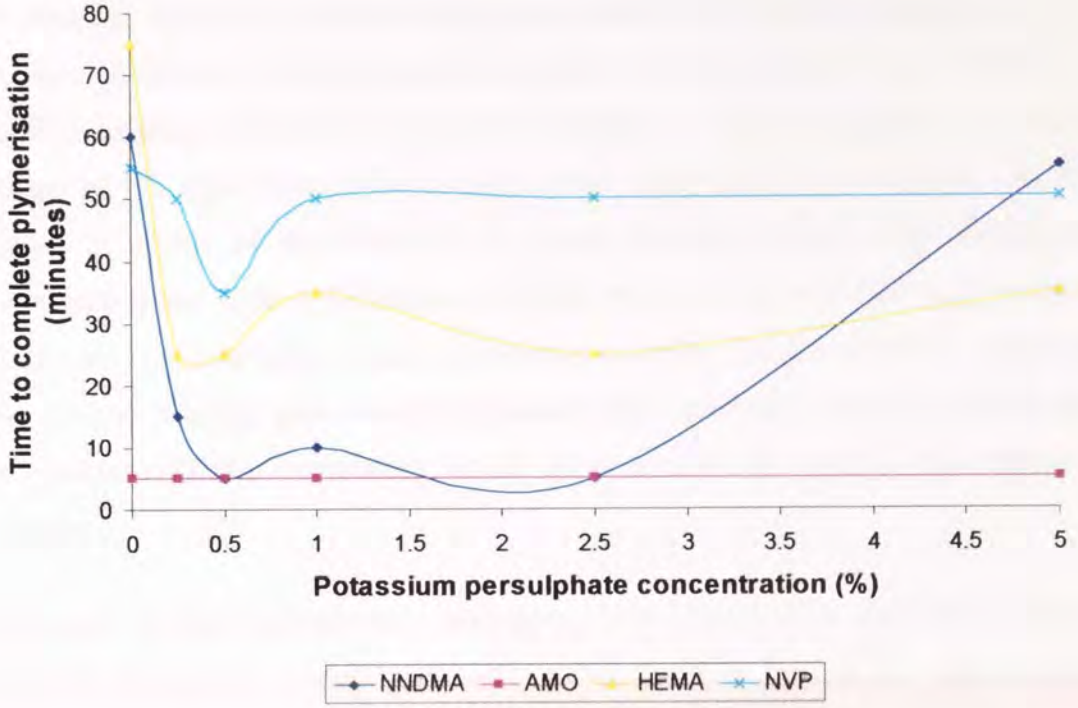


Figure 3.7 Polymerisation times of organic systems with increasing concentrations of supplementary thermal initiator (potassium persulphate)
Thermal initiator was used in addition to 0.13% (w/w) Ebacryl:Irgacure (10:3) (5 minute error bars are shown)

The use of potassium persulphate failed to give faster polymerisation times for the monomers than had previously been achieved. Though in some cases previous times were matched, there appears at this stage to be no definite advantage in use of potassium persulphate to facilitate alternative routes of polymerisation. In the case of NNDMA and AMO samples however, undissolved potassium persulphate remained after shaking, limiting the concentration of the initiator available to participate in polymerisation. It is interesting to note that in the case of NNDMA, HEMA and NVP, a deviation from the expected curve can be seen on graphs showing polymerisation times of the monomers with increasing concentrations of potassium persulphate. It seems unlikely that this is due to a true deviance of the times but rather a result of experimental error. The increase in polymerisation time seen for NNDMA and

HEMA when the greatest concentration, 5%, of potassium persulphate was used is possibly due to the production of excess initiator radicals. These react with each other rather than with the monomer chains reducing initiator radicals within the reaction, thus polymer chain lengths are reduced.

The presence of each of the solvents (water and NMP) aided dissolution of the potassium persulphate but polymerisation times were not improved. The increase in sample thickness that resulted from the addition of solvent appeared to hinder radiation of UV light through the sample to the extent that polymerisation was not initiated in many of the samples. In those samples where some degree of polymerisation did occur (NNDMA, AMO) the increased volume effectively diluted the initiator concentration again preventing complete polymerisation. Although relatively low viscosity gels would be expected with use of this volume of solvent, the gels produced in this experiment would be unsuitable for use as skin adhesive hydrogels.

The failure of the hydrophobic monomers, (VB, Butyl MA and Butyl A) to polymerise completely within practically useful times in any of the experimental conditions used so far, has led to the conclusion that these monomers are unsuitable for use in skin adhesive hydrogels. The potential of superfluous heat energy produced during photopolymerisation remains, and other thermal initiators or redox "accelerators" in conjunction with the potassium persulphate also require investigation.

3.7 Discussion

Three neutral organic monomers appeared to be useful in extending the range of chemical compositions of skin adhesive hydrogels. These were NVP, NNDMA and AMO. All three monomers show obvious structural relation to one another in that their hydrophilicity is conferred by the presence of nitrogen rather than the oxygen of the hydroxyl group of HEMA.

NVP is well known for it's low reactivity ratio in organic systems and this has been the key shortcoming of this monomer in hydrogel synthesis. The most significant observation of this work was the recognition for the first time that NVP is an acceptable monomer in terms of polymerisation rate for use in aqueous-based skin adhesive gel systems due to the increased reactivity ratio observed in aqueous systems.

VB, Butyl A, and Butyl MA demonstrated only limited degrees of polymerisation with the photoinitiator systems investigated, an unsurprising result considering their hydrophobic nature. As these monomers showed little promise of potential for increased cure with different initiator systems they were deemed unsuitable for further skin adhesive hydrogel research within this area.

Reassuringly, the photoinitiator system currently used by many within the hydrogel industry proved worthy, giving low polymerisation times compared to the other systems studied and producing good quality gels with low levels of unpolymerised residual liquid. Investigations into optimum concentrations of this photoinitiator showed levels considerably higher than those used in commercial skin adhesive hydrogel production (First Water Hydrogels Ltd) to be most effective in this laboratory. This highlights the importance of considering individual laboratory conditions, duration of exposure and light intensity as well as photoinitiator systems used in the photopolymerisation of hydrogels.

Failure of the supplementary thermal initiator system studied to improve cure times or quality was disappointing, however, the potential for use of otherwise wasted thermal

energy remains. Ammonium persulphate is a more soluble alternative thermal initiator that could be considered. Combination with redox accelerators may improve the performance of potassium persulphate as well as simultaneously eliminating any problems due to oxygen inhibition of surface polymerisation.

Chapter Four

Exploratory Studies:

Design of Adhesive Hydrogel Systems

4. Exploratory Studies: Design of Adhesive Hydrogel Systems

4.1 Introduction

In the development of an ideal skin adhesive drug delivery system it is important to recognise and understand the forces responsible for adhesive bond formation and performance. Generally, a good adhesive has to provide high adhesive and cohesive forces. Ease of flow and surface wettability of an adhesive are important in the formation of an adhesive bond between the adherend and a substrate. Cohesive strength is essential for successful mechanical transfer of force through the adhesive bond to the substrate.

This chapter explores the potential for manipulation of hydrogel composition to alter ease of application, strength of adhesion and ease of removal of partially hydrated ionic hydrogels from human skin.

4.2 Adhesive performance

Adhesive performance is controlled by a number of material properties that together result in good application and extended adhesion characteristics. Techniques that can be employed to measure these properties include tack, peel adhesion and dynamic-mechanical measurements e.g. shear strength.

The adhesion of partially hydrated hydrogels to the skin is dependent on three elements that work together to determine the suitability of a hydrogel composition for skin adhesive applications in terms of its adhesive and mechanical properties.

- The **rheological** properties of the hydrogel which determine its viscous and elastic behaviour
- A **hydrophilic** component that removes the lubricating interfacial water layer between the hydrogel and the skin
- **Hydrophobic domains** within the hydrogel interact with lipids of the skin, contributing to the adhesive bond between the hydrogel and the skin

The relationship between composition and the adhesive properties of partially hydrated ionic hydrogels was examined. Manipulation of hydrogel composition including weight fraction of the polymeric component was used to establish composition ranges for functional skin adhesive gels. These could then be used as a guide in subsequent release experiments.

4.2.1 Peel Strength Testing

Peel strength tests can be used to give an indication of the ease of removal of an adhesive from a substrate. This gives important information about the strength of the adhesive bond between the hydrogel and the skin. Peel strength tests also provide information about the relative cohesive strength of the material and the potential for cohesive failure of the material prior to adhesive failure of the bond between the hydrogel and the substrate. "Legging" of the material during testing gives further indication of the cohesive properties of the gel. Variables to consider during peel strength testing of a material include contact time and pressure, the nature of the substrate, angle of peel and peel speed.

Tests were carried out at a 90° angle, the preferred choice in testing of dermal adhesive because of the associated lower sensitivity to backing material failure (Horstmann et al). A withdrawal speed of 500mm/second was maintained throughout these experiments. The subject's forearm was cleaned with alcohol prior to each test to remove any residual adhesive and minimise lipid variation between tests. Strips of adhesive hydrogel (25mm) were applied to the subject's forearm with backing sheet in place. A 2.5Kg weight was

then rolled across the hydrogel strip to ensure that even contact pressure was applied to each sample. Peel strength tests commenced after one-minute application time.

In general, peel strength tests are carried out by measuring the resistance to peeling of an adhesive from an artificial substrate rather than a human arm. Major differences between these artificial testing surfaces and the human *Stratum corneum* make them poor models and measurements simply provide a comparative indication of the adhesive behaviour of the test sample. Samples studied in this work were peeled from the researcher's forearm in order that a more representative measure of skin adhesive behaviour could be obtained. This technique is valuable for establishing a useful indication of adhesive properties, but the subjective nature of the test must also be considered. Variations in subject skin composition will alter the adhesive performance of a material. Subjective differences in experimental technique may also influence measurements.

4.2.2 Skin stripping effects

Upon removal, most adhesives detach the upper stratum corneum layer after a few seconds of skin contact. This is known as the stripping effect (Horstmann et al, 1999). As a result, reapplication of detached dermal adhesives is rarely possible and application of a fresh adhesive device is necessary. The effect of skin damage during removal of the adhesive on the delivery of release agents from subsequent applications is an important consideration. Increased transdermal delivery of a compound may be detrimental to its effectiveness or even give rise to toxic dosage levels.

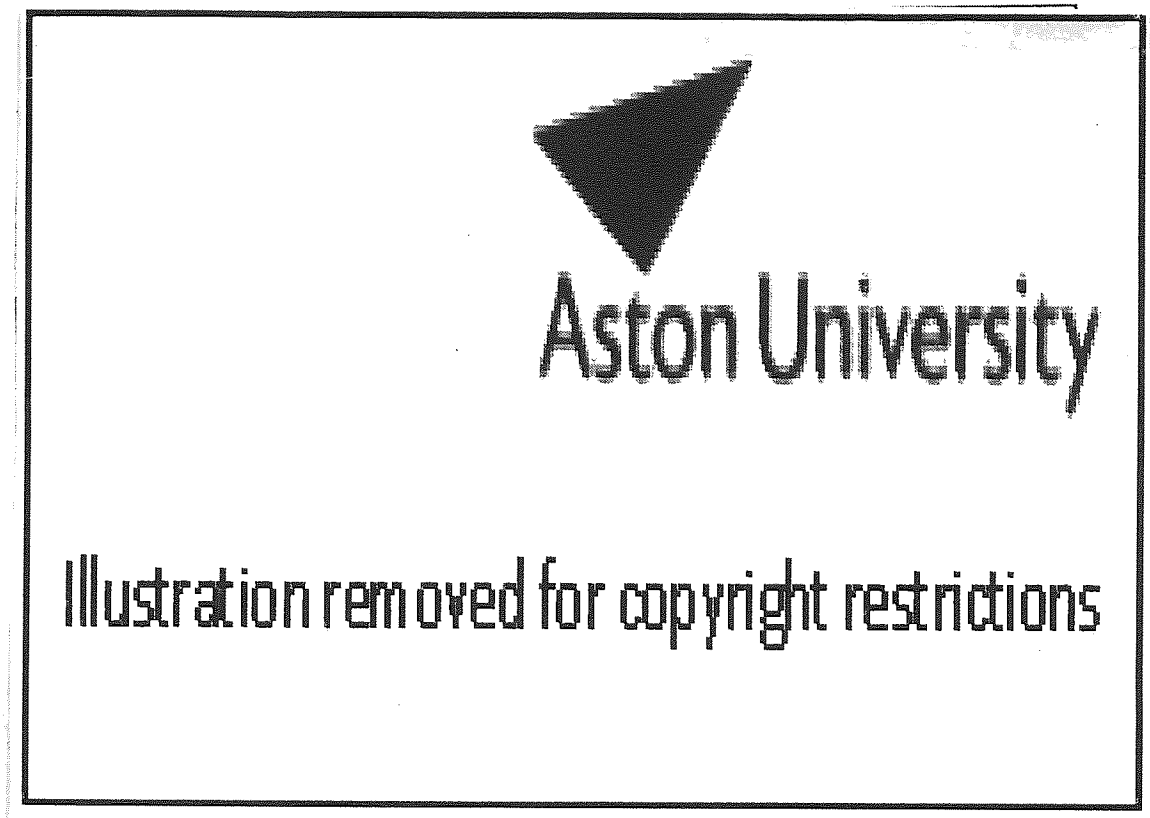


Figure 4.1 Schematic diagram of detachment of skin by removal of an adhesive patch *(Horstmann et al, 1999)*

Trauma to the skin upon removal of an adhesive device is difficult to quantify but is an important consideration in the assessment of suitability of a skin adhesive hydrogel for medical use. The effects of single and multiple applications of a range of current commercial adhesive medical tapes were compared with those of skin adhesive hydrogels using Scanning Electron Microscopy (SEM). Removal of outer epidermal cells was used as a guide to the degree of skin trauma caused by removal of the hydrogel.

4.2.3 Rheological properties

Rheological performance of skin adhesive hydrogels under oscillatory conditions give an insight into the likely behaviour of a material when stressed at the different frequencies employed in application and removal of the device. The viscoelastic response of a hydrogel depends on the nature (magnitude and duration) of the imposed mechanical

stress. An applied mechanical stress leads to a time dependent strain response of the material as the polymer chains move. Recovery time upon removal of the applied force can be used to quantify the elastic and viscous components of the material (Anseth et al, 1996).

Viscous flow of the material when stressed at low frequencies such as those used in application to the skin determines how easily the hydrogel can be applied and promotes intimate contact between the adhesive and the adherend necessary for bond formation. The parameter is difficult to quantify but the earliest attempt, made by Dahlquist produced the criterion that now bears his name (Venkatraman & Gale, 1998).

The Dahlquist criterion for the modulus of a successful pressure sensitive adhesive:

$$\text{Modulus of adhesive} < 10^6 \text{ dyn cm}^{-2} \qquad \text{Equation 4.1}$$

The elastic properties of a hydrogel at the high frequency stresses involved in its removal reflect its ability to peel away cleanly and in one piece without leaving behind an adhesive residue. These qualities are related to the cohesive strength of the hydrogel relative to the strength of its adhesion to skin (Venkatraman & Gale, 1998).

The viscoelastic properties of the partially hydrated hydrogels were measured using a Bohlin CVO rheometer, as described in section 2.4. Elastic (G') and viscous (G'') moduli of the samples at frequencies of around 1Hz and 10Hz were examined as approximations to the conditions of application and removal of the hydrogel respectively. Good cohesive properties in application can be expected from hydrogels with an elastic modulus (G') of between 10^3 and 10^5 Pa and a viscous modulus of between 10^2 and $5x10^3$ Pa, although these values can only be used as a guide. Actual handling characteristics of the hydrogels should also be considered in deciding their suitability for skin adhesive applications. The ratio of the viscous component (G") to the elastic component (G') (tan ∂) should always be less than 1 i.e. the hydrogels should always have a dominant elastic component.

4.3 Components of an adhesive hydrogel

4.3.1 Key components of an adhesive hydrogel

Partially hydrated (skin adhesive) hydrogels consist of three main components:

- **Unsaturated water soluble monomer**

  The backbone polymer of the hydrogel forms the cohesive basis of the material. An ionic monomer component is essential for production of adhesive partially hydrated hydrogels. The hydrophilic nature of ionic monomers imparts a high affinity for water upon the hydrogel, which plays an important role in adhesion (as described in section 1.5.1). The functional groups of ionic monomers are also important in their influence on hydrogel properties. Ionic monomers 2-acrylamido-2-methylpropane sulphonic acid, used in the form of its sodium salt (NaAMPS), and the potassium salt of 3-sulphopropyl acrylate (SPA) were the focus of work within this chapter. Copolymerisation of both monomers with the neutral monomers studied in chapter 3 of this thesis broadened the scope for manipulation of partially hydrated hydrogel properties to suit specific applications.

- **Glycerol**

  The polar groups within glycerol interact strongly with the water within the hydrogel, reducing the effects of evaporation. This is sometimes referred to as humectant behaviour. Glycerol also acts as a plasticiser and has been shown to influence cohesion of the hydrogel (Fleming, 1999). Plasticisers within polymers can be used as a convenient means of adjusting the tackiness and wetting behaviour of the material surface (Horstmann et al, 1999).

- **Water**

  Water also acts as a plasticiser within the hydrogel. By swelling the hydrogel the water increases the volume within the material, facilitating rotational movement of the polymer chains. Translational mobility will be impeded to an extent dependent on

the degree of covalent crosslinking within the hydrogel (Ratner, 1986). Water is also important as a transport medium for the diffusion of solutes across the hydrogel. Partial hydration of the hydrogel ensures that the material retains its high residual capacity for water (the hydrophilic constituent monomer produces a high EWC hydrogel) that promotes adhesivity of the hydrogel to the skin.

As detailed in chapter 3 of this thesis, photopolymerisation of the unsaturated monomers in a mixture of these constituents to produce a hydrogel network requires the presence of small concentrations of photoinitiator and crosslinking agents within the composition at the time of polymerisation.

4.3.2 Ionic monomers

The hydrogel compositions studied in this chapter of work are homo- and co-polymers of the ionic monomers, SPA and NaAMPS. These particular ionic monomers were chosen as a basis for exploratory studies of the manipulation of partially hydrated hydrogel properties. Both monomers have been successfully used in the production of skin adhesive hydrogels for commercial applications. Structures of the ionic and neutral monomers used in the homo- and co-polymers studied here are shown in section 2.2

4.4 Aims of this chapter

Development of hydrogel release systems is dependent on the modification of hydrogel properties to suit an application. In addition to the necessary diffusion and release characteristics required, as discussed in later chapters, it is important that placement of the device is simple and can be maintained for the duration of its functional life. The adhesive properties of partially hydrated ionic hydrogels provide an integral means of attachment of the device to the dermal treatment site.

Adhesion of a hydrogel to the skin has been described as a three-component phenomenon. Each of the components is a function of the composition of the hydrogel and as such can be influenced by modification of the composition. This chapter is concerned with the manipulation of hydrogel composition to modify adhesion characteristics of partially hydrated hydrogels for use in dermal applications.

The suitability of a hydrogel for skin adhesive applications can be judged by its physical characteristics. Peel strength and rheological measurements, for example, can be used as indications of the adhesive behaviour of a hydrogel at the point of application, during application and at the time of removal. Changes in these parameters with alterations to hydrogel composition and crosslinking systems were studied.

The effects of crosslink density on hydrogel characteristics were investigated by the use of a range of concentrations of crosslinking agents and multi-functional crosslinking systems. Results were used to identify parameters for suitable polymer systems, for use in the development of skin adhesive hydrogels within this laboratory.

The potential for copolymerisation of ionic monomers SPA and NaAMPS with some of the neutral monomers studied in chapter 3 of this thesis were investigated, with the aim of broadening the palette of skin adhesive hydrogels available for the development of hydrogel release systems. Mechanical properties of these hydrogels were used to identify the influence of monomer properties and functional groups on the properties of a hydrogel.

In the development of diffusion-based release systems, identification of the upper and lower limits for water volume fraction without loss of structural integrity is useful. The influence of polymer volume fraction on hydrogel properties was studied with respect to acceptable composition boundaries for the production of cohesively stable adhesive hydrogels.

It was hoped that investigations of the influence of the different components of a hydrogel system on its adhesion characteristics would provide information on the potential routes for modification of hydrogel characteristics for clinical applications.

4.5 Results

4.5.1 Partially hydrated hydrogel compositions

Recent patents (Jevne et al, 1986, Munro, 2002, Feldstein et al, 2002) can be used to give broad indications of composition requirements for the production partially hydrated hydrogels. However, these give no details regarding the changes to hydrogel characteristics at specific component contents. Previous work within this laboratory (Fleming, 1999) has defined the upper and lower limits of the three key components of skin adhesive hydrogels; monomer, water and humectant/plasticiser for the production of cohesive, adhesive hydrogels. A series of simple NaAMPS hydrogels were produced at different monomer, water and glycerol ratios. The associated characteristics of these hydrogels are shown in figure 4.2 and can be used as a guide in the development of new partially hydrated compositions.

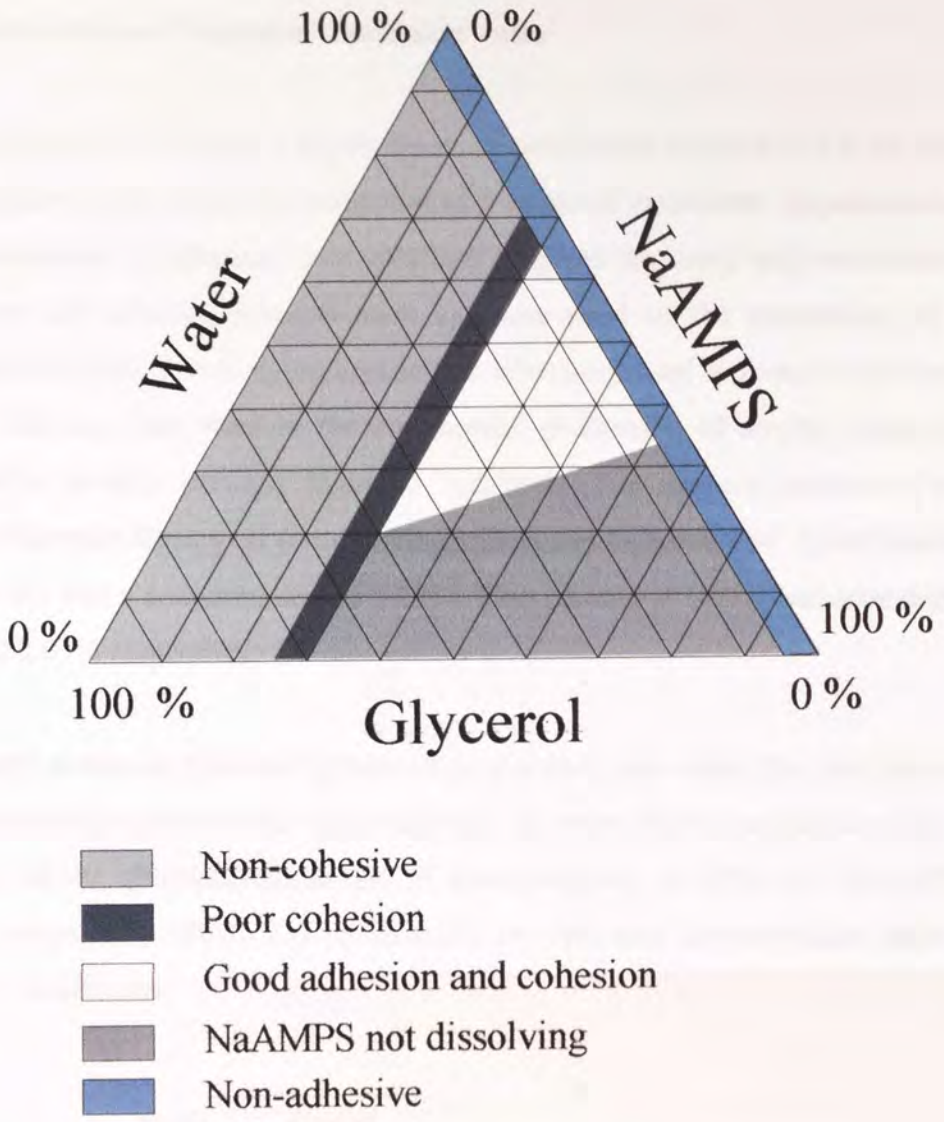


Figure 4.2 Triangular graph revealing the properties created from various monomer, glycerol and water compositions (w/w)

A composition from within the area of this triangle that denotes those hydrogels with good adhesive and cohesive properties was chosen as a starting point for these studies. As described previously, the compositions investigated within this chapter of work are based on ionic monomers (SPA and NaAMPS) and include glycerol as a humectant/plasticising agent. Details of the chosen starting point composition are shown below.

Ionic monomer	40%
Water	35%
Glycerol	25%

4.5.2 Optimisation of Initiator/crosslinker ratio

Results discussed in chapter 3 of this thesis demonstrated Irgacure 184 to be an efficient photoinitiator in the photopolymerisation of a range of monomers. Experimental studies gave indications of optimum concentrations required for rapid polymerisation of bulk monomers and solvated systems such as those used in the production of partially hydrated hydrogels. Previous workers in this laboratory used a photoinitiator/crosslinker mixture that has been used in the commercial production of similar compositions to successfully produce partially hydrated hydrogels. The mixture consists of an epoxy acrylate oligomer, Ebacryl II (crosslinking agent) and Irgacure 184 (photoinitiator), at a ratio of 10:3 and a concentration of 0.13%. This equates to individual concentrations of 0.1% and 0.03% respectively.

Preliminary studies in this work produced poor quality gels when the same concentration of the photoinitiator/crosslinker mix was used. A range of concentrations of the mixture was used in the photopolymerisation of homopolymers of SPA and NaAMPS at the chosen composition (40:35:25) to establish an optimum concentration under current laboratory conditions.

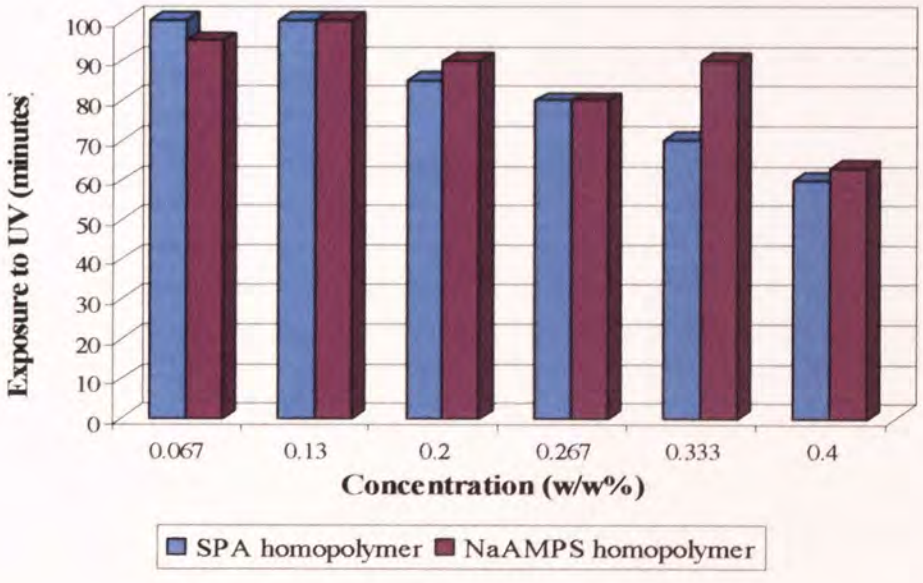


Figure 4.3 Polymerisation times with increasing mixed photoinitiator/crosslinker concentration.

Ebacryl II (crosslinking agent) and Irgacure 184 (photoinitiator), were used at a ratio of 10:3.

Figure 4.3 shows the UV exposure times required for each of the samples to polymerise to form low viscosity, non-cohesive gels. Polymerisation times were reduced with increasing concentration of Ebacryl/Irgacure 184 mixture. Extension of exposure times failed to produce more cohesive hydrogels. These results contrast with the successful production of SPA and NaAMPS copolymer hydrogels for commercial applications using this crosslinker/initiator system. Although laboratory conditions will play a part in influencing the photopolymerisation process, the structures of SPA and NaAMPS (shown in section 2.2.1) can be used to explain these results. Polymerisation of the monomers as homopolymers produces long polymer chains of covalently linked monomer molecules. Dipolar and hydrogen bonding between complementary functional groups of the two monomers when copolymerised produce interchain linkages between the polymer chains, strengthening the effective three-dimensional network formed and producing more cohesive gels.

4.5.3 Copolymers of SPA and NaAMPS

4.5.3.1 Copolymer compositions

The increased cohesive network produced by copolymerisation of SPA and NaAMPS has been successfully used in commercial applications of hydrogels. Identification of an extended range of monomers suitable for copolymerisation with hydrophilic monomers to produce skin adhesive partially hydrated hydrogels is desirable in the development of skin adhesive hydrogels for clinical applications. More extensive capability for modification of partially hydrated hydrogels and their properties will increase the potential for design of hydrogel release systems.

Copolymers of SPA and NaAMPS with each other and with neutral monomers (successfully photopolymerised in chapter three of this thesis) were produced and the mechanical properties of the hydrogels were compared. Samples were prepared, according to section 2.3.2, at a composition of (40:30:30), comparable to that studied previously. All subsequent work within this chapter was carried out on partially hydrated hydrogels produced by the moving web technique described in section 2.3.2. The monomer component of the composition constituted a 50:50 ratio of the two component monomers of the copolymer. An elevated concentration of crosslinker/initiator mix (0.33%) was used to compensate for the decreased polymerisation of SPA and NaAMPS homopolymers observed previously.

Descriptions of the copolymer hydrogels are detailed in table 4.1. These were used alongside quantitative experimental results to assess the suitability of each composition for skin adhesive applications and to evaluate the effects of system manipulation on mechanical properties of the hydrogels.

Copolymer	Description of hydrogel
NaAMPS/SPA	Best handling characteristics of all copolymers studied. No surface residue or odour.
NaAMPS/NVP	Good handling characteristics. Slight odour of NVP monomer.
NaAMPS/NNDMA	Good handling characteristics, noticeable elasticity. No surface residue or odour.
NaAMPS/AMO	Low cohesive strength. No odour
SPA/NVP	Very low cohesive strength, opaque gel. Strong odour and surface residue.
SPA/NNDMA	Noticeable elasticity. Slight surface residue.
SPA/AMO	Slightly low cohesive strength. Strong odour

Table 4.1 Descriptions of copolymer handling characteristics

4.5.3.2 Rheological properties of copolymers

Rheological measurements of the samples were taken using a Bohlin CVO rheometer according to the technique described in section 2.4.1 of this thesis. Elastic (G') and viscous (G") behaviours of the copolymers were compared. Viscoelastic behaviour at low frequency (~1Hz) and at a higher frequency (~10Hz) was measured to represent application and removal conditions that the hydrogel may be subjected to during clinical use. Measured elastic and viscous responses at these frequencies are shown in figures 4.4 and 4.5.

During application of the hydrogel a strongly dominant elastic component is necessary to allow flow of the material to form a close fit with the skin. At low frequency stresses (1Hz) such as those the hydrogel will be subjected to during application, a reduced viscous component is important. The viscoelastic response of the hydrogel to higher frequency stresses (10Hz), such as those experienced during removal of the hydrogel, is important in facilitating clean removal of the material in one piece. An increased viscous component and a reduction in the elastic component will avoid legging of the hydrogel. A tan δ value of less than 1 must be maintained however, to avoid brittle breakage of the hydrogel under high frequency stresses.

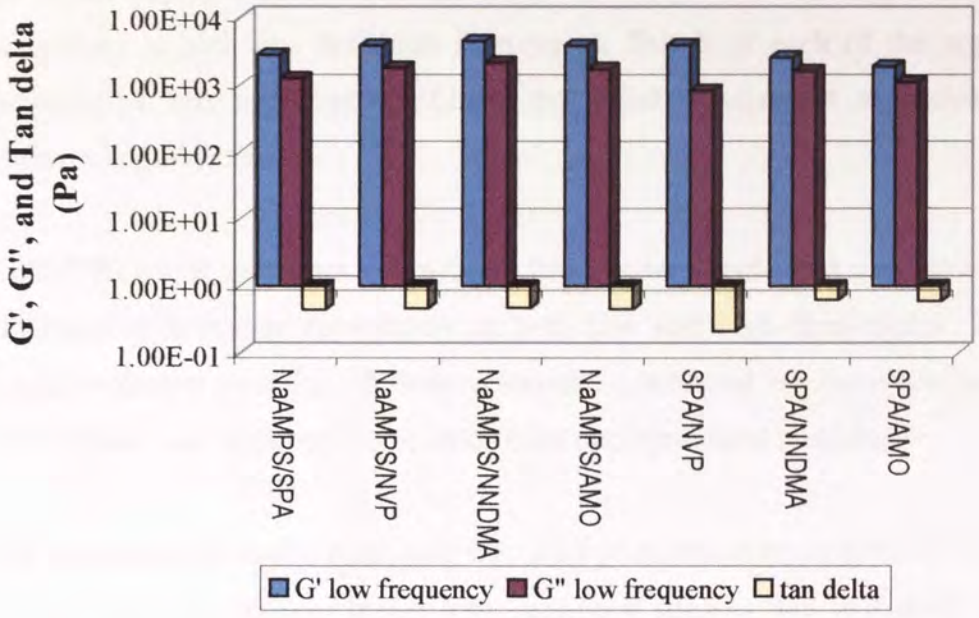


Figure 4.4 Rheological properties of SPA and NaAMPS copolymers (50:50) at low frequency (1.1Hz)

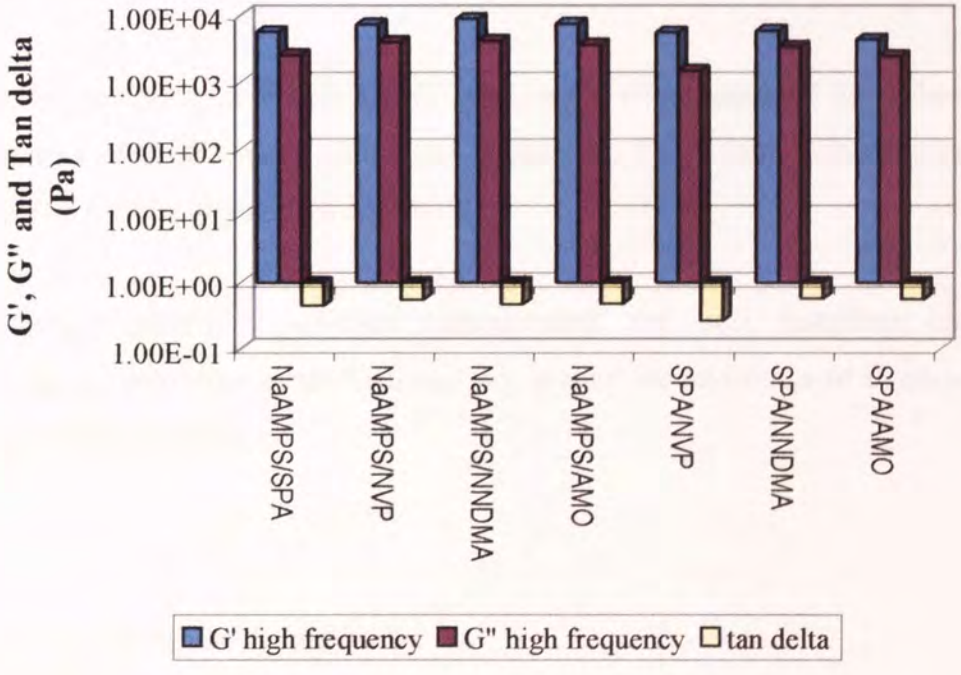


Figure 4.5 Rheological properties of SPA and NaAMPS copolymers (50:50) at high frequency (10 Hz)

All of the copolymers had dominant elastic components with respect to their viscous component at both low and high frequencies. Tan δ of each of the copolymers will therefore be less than one, fullfilling the initial requirement of hydrogels for skin adhesive applications.

NaAMPS/neutral monomer copolymers had greater elastic and viscous responses than SPA/neutral monomer copolymers at both low and high frequencies. This indicates greater cohesive stability of these materials, confirmed by their preferable handling characteristic and the absence of odour from unpolymerised monomer.

The dominance of elastic behaviour was most pronounced in the SPA/NVP copolymer in its low viscous response. Under low frequency stresses this will result in very good compliance of the hydrogel to the skin but at high frequency stresses the observed legging of the gel may cause problems. The low cohesive strength of this composition during handling may be a result of incomplete polymerisation. The strong odour and opaque appearance of the hydrogel which were noted suggest that unpolymerised monomer remained within the sample, resulting in poor network formation and low cohesive strength.

With the exception of the SPA/NVP coploymer, copolymers of SPA showed reduced dominance of their elastic component (higher tan δ) in their reduced elastic response compared with copolymers of NaAMPS.

The SPA/NaAMPS copolymer demonstrated the best handling characteristics. Rheologocal behaviour of the hydrogel was around the mid-range of those seen with this group of compositions.

4.5.3.3 Peel strengths of copolymers

Peel strengths for each of the copolymer compositons were measured according to method 2.4.2. Tests were repeated and the mean of the average peel strengths measured in each test are shown (figure 4.6) for each composition.

A target peel strength of 3 N/25mm (for adhesion to human skin) has been suggested for the use of partially hydrated hydrogels in dermal applicastions, following research by First Water Hydrogels Ltd. This has been shown in external human trials to ensure stable adhesion of the hydrogel for extended time periods and is associated with minimal discomfort upon removal of the hydrogel.

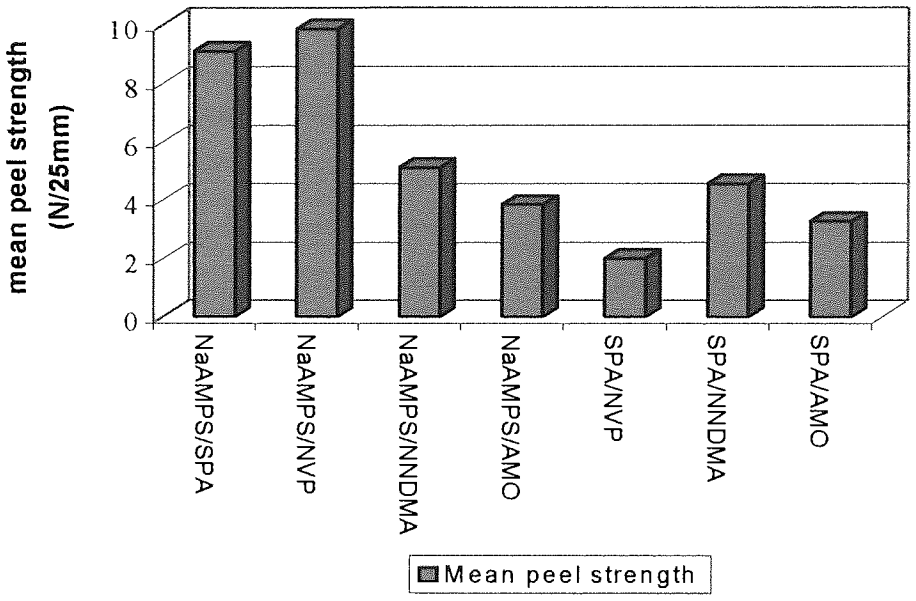


Figure 4.6 Mean peel strength of 50:50 copolymers

Lower average peel strengths were measured for SPA copolymers than for the respective copolymers of NaAMPS. In the case of samples where the presence of residuals on the hydrogel surface was noted the residual liquid at the interface between the hydrogel and the skin will hinder the formation of adhesive bonds. The SPA/NVP copolymer had the lowest peel strength as a result of the strong presence of residuals at the polymer surface.

The peel strengths of NaAMPS/SPA and NaAMPS/NVP copolymers were particularly high and are associated with the experience of considerable pain by the patient upon removal of the hydrogel.

Mean peel strengths of the other copolymer samples were around the target strength of 3N/25mm, providing adequate adhesion and minimal skin trauma and pain upon removal.

4.5.4 Tri-functional initiator system (PETA)

The reduced cohesive strength of SPA based copolymers relative to similar NaAMPS-based copolymers is possibly in part a result of reduced hydrogen bonding between the chains and therefore a reduced effective network formation within these polymers. The presence of odour and/or slight surface residuals in each of the SPA copolymers also suggests incomplete polymerisation of the monomer and possibly incomplete or ineffective crosslinking of the co-monomers in the polymer chains. Use of a tri-functional crosslinker, pentaerithritol triacrylate (PETA) to increase crosslink density of the hydrogel was therefore investigated. The increased functionality of this crosslinker compared to Ebacryl II (bis-functional) may modify the polymer network without the need for increased crosslinker concentration within the composition.

A 10:3 ratio mixture of crosslinker: photoinitiator was prepared and used at a concentration of 0.33% for photopolymerisation of each of the copolymers being studied. Samples of four of the copolymer compositions were prepared according to method 2.3.2. Table 4.2 details the handling characteristics of the hydrogels produced with this crosslinking system.

Copolymer	Description of hydrogel
NaAMPS/SPA	Low cohesive strength, poor adhesive properties
NaAMPS/NVP	Very low cohesive strength, slightly adhesive
NaAMPS/NNDMA	Very low cohesive strength, hydrogel quite tacky
NaAMPS/AMO	Sufficiently cohesive for handling, slightly adhesive
SPA/NVP	Poor adhesive properties
SPA/NNDMA	Low cohesive strength, moderately adhesive
SPA/AMO	Low cohesive strength, slightly adhesive

Table 4.2 Handling characteristics of co-monomer mixtures (50:50) photopolymerised in the presence of a PETA trifunctional crosslinking system.

As described in table 4.2, all of the copolymers produced in the presence of 0.33% PETA/Irgacure 184 (10:3) had low cohesive strengths. The increase in crosslink density compared with that of the same copolymers when produced in the presence of the same concentration of Ebacryl/Irgacure 184 (10:3) produced hydrogels with a significantly reduced elastic component. This produced materials with low cohesive strength that were subject to brittle breakage during handling and prevented the water uptake and polymer chain rotation necessary for adhesion. As a result of the poor handling characteristics of the hydrogels mechanical measurements were not taken.

4.5.5 Decreased ratio crosslinker:photoinitiator

The observed lack of adhesive characteristics and brittle nature of copolymers produced in the presence of the tri-functional crosslinker system are likely to have been a direct result of a marked increase in effective crosslink density within these compositions. A new ratio of tri-functional crosslinker to photoinitiator (5:3) was used with the same compositions as a means of decreasing crosslink density without impeding the polymerisation process by reduction of photoinitiator concentration.

Rheological properties of the hydrogels produced with this lower ratio of PETA:Irgacure 184 (5:3) are shown in figures 4.7 and 4.8.

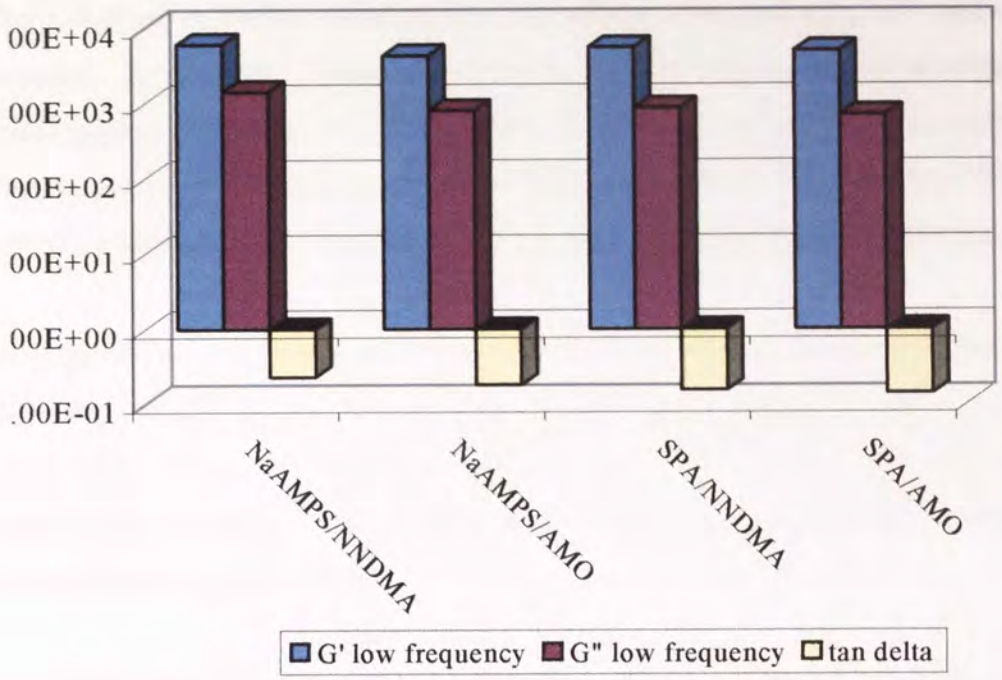


Figure 4.7 Rheological properties (at 1 Hz) of SPA and NaAMPS copolymers crosslinked with PETA at a modified PETA:Irgacure 184 ratio (5:3)

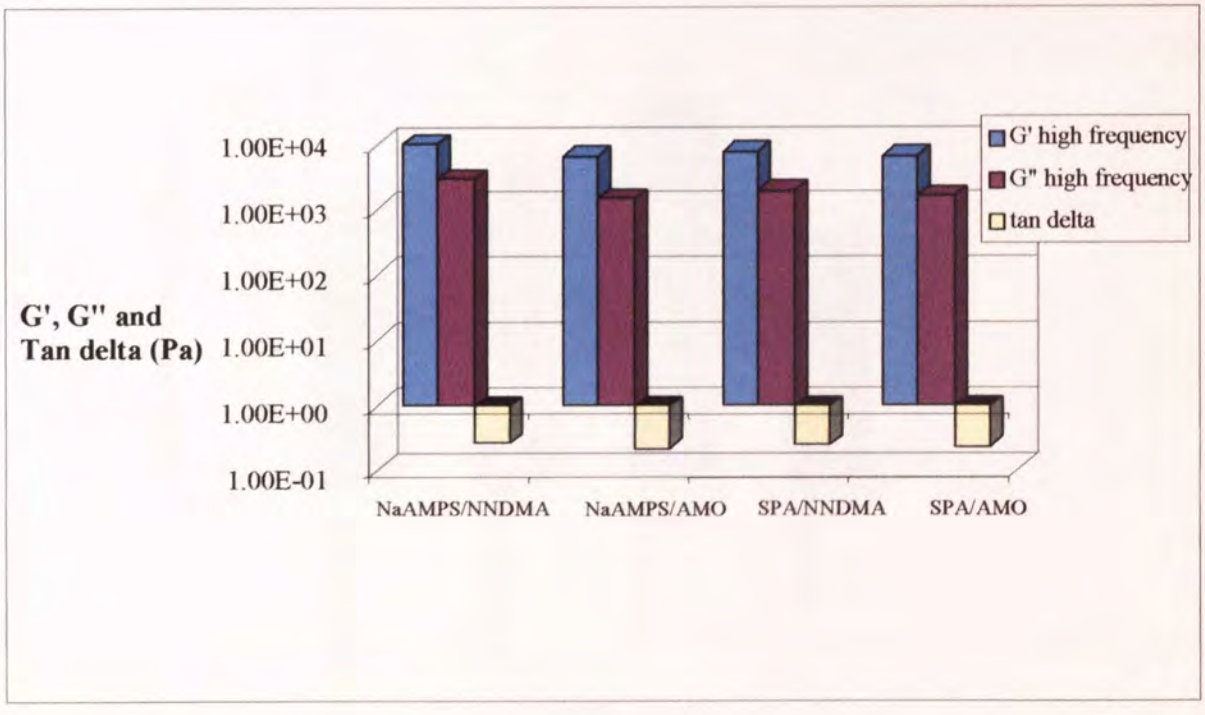


Figure 4.8 Rheological properties (at 10 Hz) of SPA and NaAMPS copolymers crosslinked with PETA at a modified PETA:Irgacure 184 ratio (5:3)

The reduction in PETA concentration was effective in producing hydrogels with lower crosslink density than those described in section 4.5.4, as demonstrated by their rheological characterisation. Tan δ values for all of the copolymers were noticeably low. This was due to the particularly low viscous response of the materials. The dominant elastic component produced hydrogels with reasonable handling characteristics.

In contrast to previous experiments, the copolymers of NaAMPS had viscoelastic characteristics comparable to those of the SPA copolymers. Overall, responses were lower than those of copolymers produced in the presence of the bi-functional crosslinking system, and the hydrogels demonstrated more brittle behaviour at high frequencies as a result.

The influence of the tri-functional crosslinker is most apparent in its effect on the peel strengths of the copolymers (figure 4.9). Mean peel strength values for the copolymers are much lower than those observed for the compositions when polymerised with Ebacryl II. It is unlikely that such low peel strengths would be sufficient to maintain placement of the hydrogel for any extended period of time.

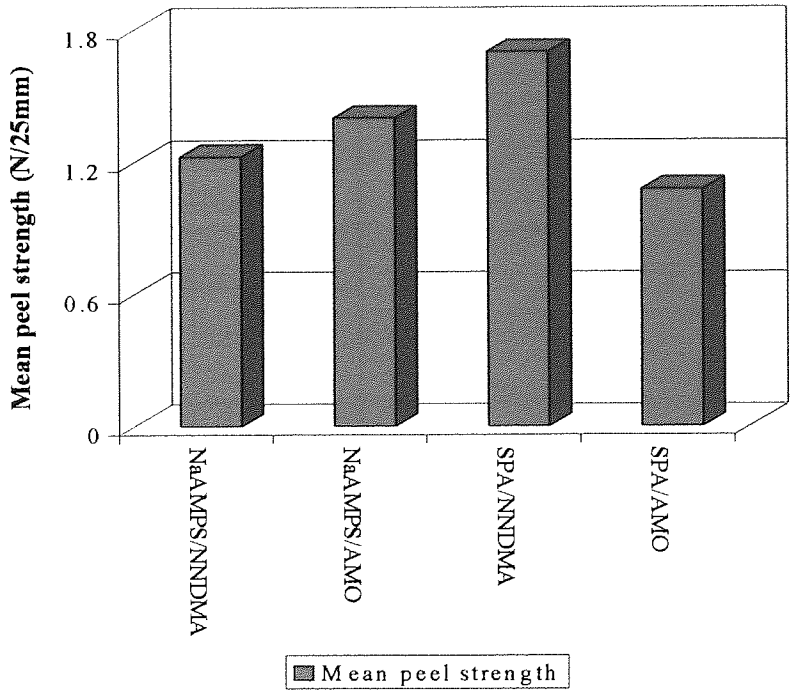


Figure 4.9 Mean peel strength of copolymers produced in the presence of PETA:Irgacure (5:3) crosslinking system

4.5.6 Co-monomer ratios

Copolymers of SPA and NaAMPS have demonstrated good adhesion characteristics and cohesive strength throughout this investigation. The investigation, described previously, of the potential of copolymerisation of NaAMPS and SPA with non-ionic hydrophilic monomers has not proved to be a readily exploitable route to a more versatile family of skin adhesive hydrogels. The next stage in this investigation is to explore the potential of copolymerising SPA and NaAMPS together. In the investigation of copolymerisation to this point, copolymers of the monomers have consisted of equal proportions of each monomer. On the basis of an overall composition of 40:35:25, monomer:water:glycerol, a range of SPA/NaAMPS copolymers were produced at different ratios of the two monomers. The mechanical characteristics of the hydrogels were examined and presented relative to those of the homopolymers of the dominant constituent monomer,. Composition details are shown in table 4.3 below.

Monomer ratio	% SPA	% NaAMPS
NaAMPS	0.0	100.0
S:N,1:3	25.0	75.0
S:N,3:5	37.5	62.5
S:N,1:1	50.0	50.0
S:N,6:4	60.0	40.0
S:N,5:3	62.5	37.5
S:N,3:1	75.0	25.0
SPA	100.0	0.0

Table 4.3 Percentage ratios of SPA and NaAMPS used in copolymers of the ionic monomers

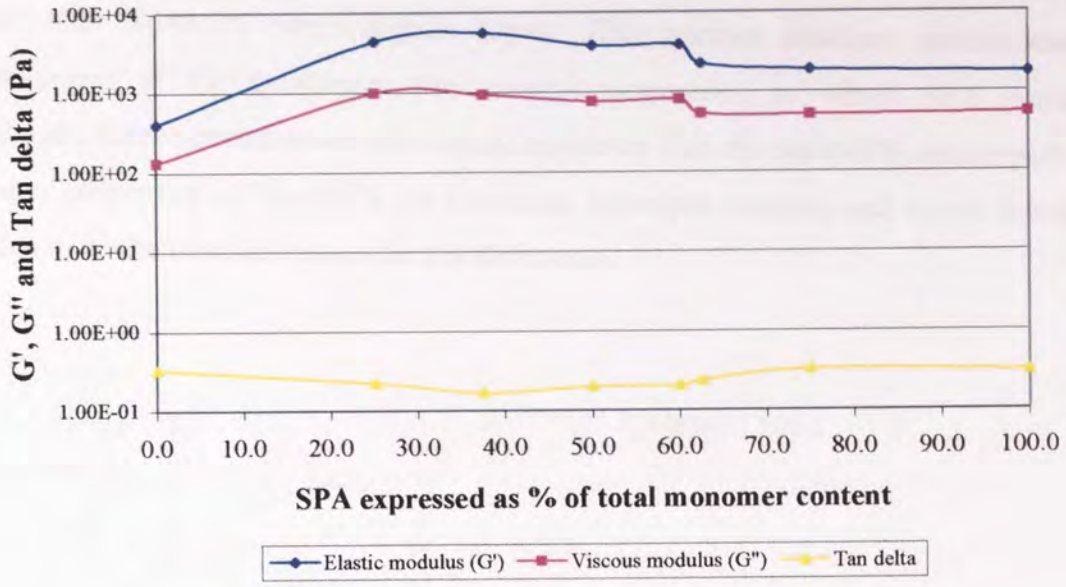


Figure 4.10 Rheological properties of NaAMPS:SPA copolymers (at 1 Hz)

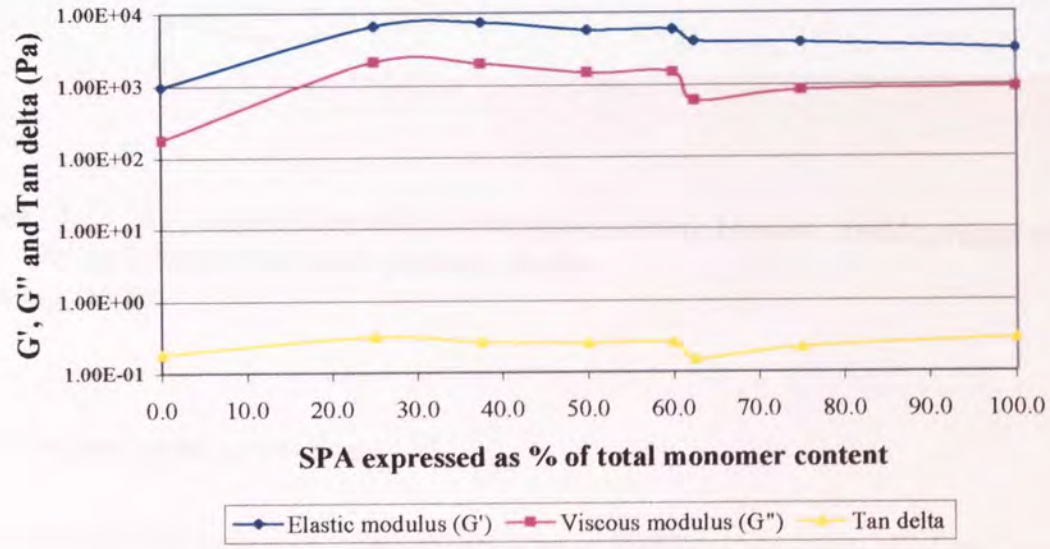


Figure 4.11 Rheological properties of NaAMPS:SPA copolymers (at 10 Hz)

As observed during preliminary experiments, copolymers of SPA and NaAMPS demonstrate rheological behaviour considerably better suited to the clinical use of the hydrogels as skin adhesives than do homopolymers of the monomers. The poor handling characteristics of homopolymers of these monomers are reflected in their rheological characteristics. Viscoelastic responses of the copolymers were similar for each of the

compositions that were dominated by NaAMPS. Values for copolymers containing less than 40% NaAMPS were slightly lower. This mirrors previous results seen for copolymers of the monomers with neutral monomers, in which SPA dominated hydrogels demonstrated lower rheological responses than the NaAMPS counterparts. The greater propensity of NaAMPS for interchain hydrogen bonding and dipole interaction seems to be the obvious reason for this difference.

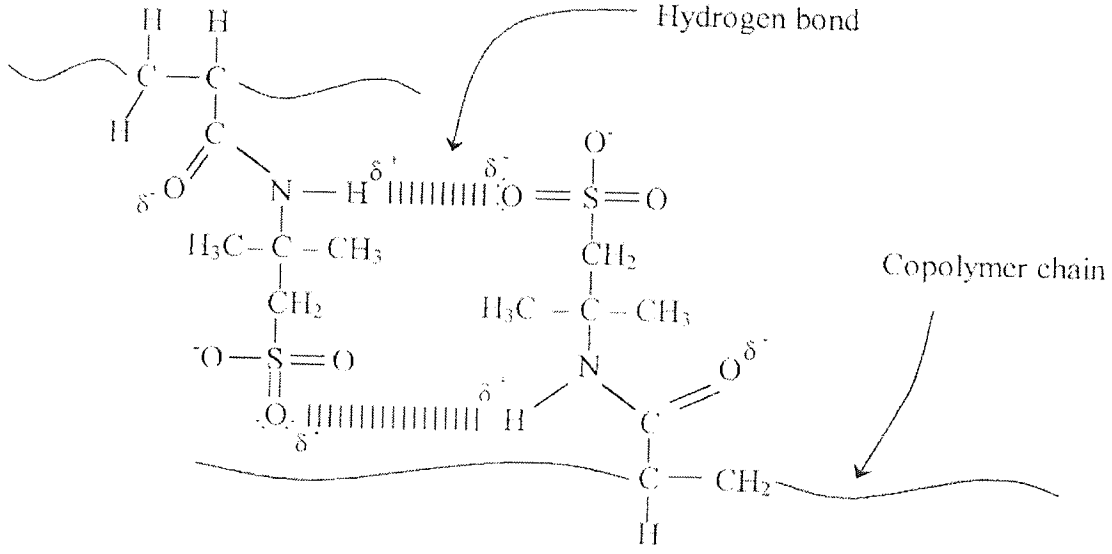


Figure 4.12 The proposed interchain hydrogen bonding between Amide groups of NaAMPS molecules on opposite polymer chains
(Benning, 2000)

4.5.7 Polymer volume fraction

The adhesive and cohesive characteristics of a hydrogel can also be influenced by modification of the bulk composition. As mentioned previously, the partially hydrated hydrogels in this study consist of 3 main components; a water-soluble monomer component, glycerol and water. Each plays a role in determining the behavioural characteristics of the hydrogel, including those of adhesion and cohesion. Alterations to the volume fractions of these components result in changes to the hydrogel characteristics.

The choice of polymer backbone has been shown in section 4.5.3 to strongly influence both cohesive and adhesive behaviour of the hydrogel. Changes to the volume fraction of monomer present within the material are likely to modify the influence of the polymeric component.

A SPA/NaAMPS copolymer (6:4) that demonstrated good handling characteristics in previous experiments was chosen as a starting point for the investigation into the control of hydrogel properties by the polymeric component of the material. The study was two-fold; firstly the glycerol component of the hydrogel was maintained at a constant level whilst monomer and water content of the material were varied either side of the composition previously studied. In the second stage of the study, the water volume fraction of the hydrogel was maintained and monomer/glycerol contents were varied. All samples were produced according to method 2.3.2 in the presence of 0.33% crosslinker/initiator (Ebacryl II/Irgacure 184, 10:1). The handling characteristics of the hydrogels are detailed in tables 4.3 and 4.4

4.5.7.1 Variation of polymer fraction at static glycerol concentration

The handling characteristics of the copolymer compositions improved with increasing polymer volume fraction. At monomer concentrations less than 35% (water>40%) residual liquid was observed on the hydrogel surface, preventing adhesive bond formation between the hydrogel and skin. As monomer concentration was increased (water concentration decreased) above 40%, the hydrogels produced demonstrated good handling characteristics with apparent adhesive and cohesive integrity.

Monomer (%)	Water (%)	Glycerol (%)	Eb II/ Irgacure 184	Description
20	55	25	0.33	Some residuals on surface
25	50	25	0.33	Some residuals on surface
30	45	25	0.33	Some residuals on surface
35	40	25	0.33	Slight residuals to touch
40	35	25	0.33	Cohesive, adhesive gel
45	30	25	0.33	Cohesive, adhesive gel
50	25	25	0.33	Cohesive, adhesive gel
55	20	25	0.33	Cohesive, adhesive gel

Table 4.4 Handling characteristics of hydrogels with increasing ratio monomer:water

Rheological evaluation of the compositions showed increasing elastic (G') and viscous (G") responses at both stress frequencies examined, as polymeric component was increased. Though viscous and elastic components neared the lower limits of the recommended ranges for these parameters in hydrogels for skin adhesive applications, all of the hydrogels were cohesive and demonstrated good handling characteristics. The presence of residual liquid on the surface of those compositions with high solvent concentrations (>60%) prevented adhesive bond formation and was the limiting factor to their use in adhesive applications.

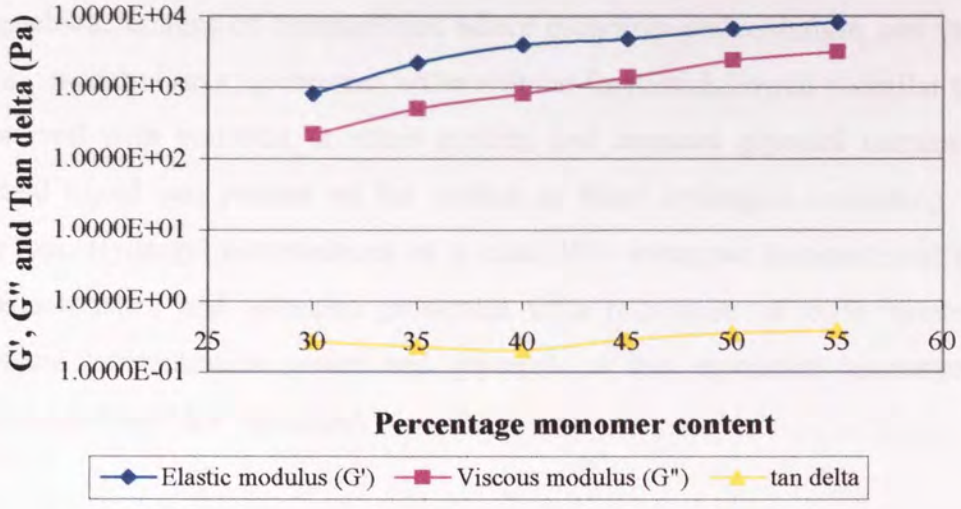


Figure 4.13 Rheological properties (at 1Hz) of 60:40 SPA:NaAMPS hydrogels with increasing ratio monomer:water

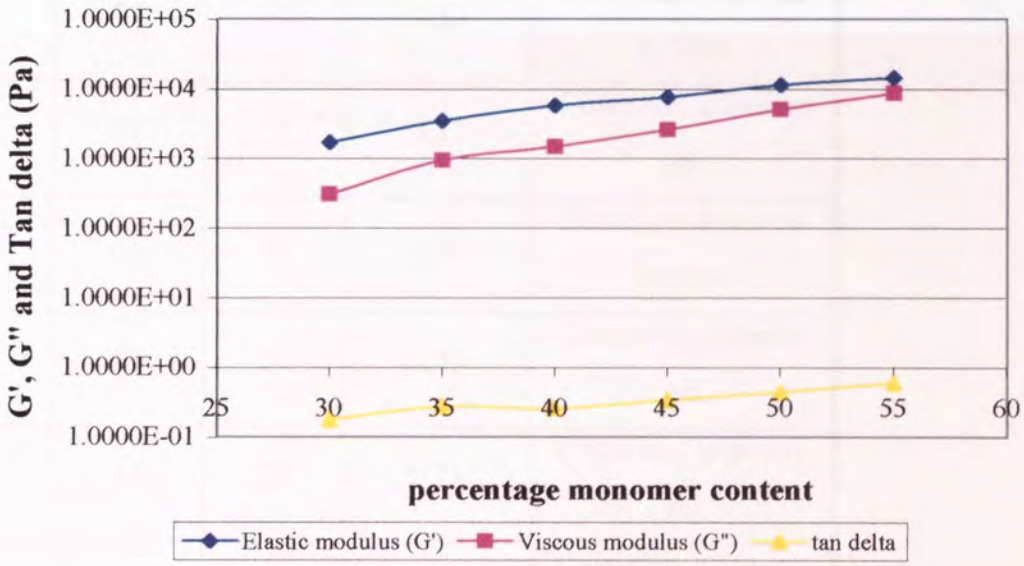


Figure 4.14 Rheological properties (at 10Hz) of 60:40 (SPA:NaAMPS) hydrogels with increasing ratio monomer:water

4.5.7.2 Variation of polymer volume fraction at static water concentration

The handling characteristics of compositions where monomer concentration was varied with glycerol concentration at a constant water volume fraction followed a similar trend to those observed with variation in water content and constant glycerol content. As before, residual liquid was present on the surface of those hydrogels containing 35% monomer or less. Hydrogel compositions of at least 40% monomer demonstrated good handling characteristics and adhesive properties to a maximum of 60% monomer. Reduced solvent concentration (water and glycerol) at this monomer concentration produced a cohesive but "dry" hydrogel.

Monomer (%)	Water (%)	Glycerol (%)	Eb II/ Irgacure 184	Description
20	35	45	0.33	Some residuals on surface
25	35	40	0.33	Some residuals on surface
30	35	35	0.33	Cohesive, adhesive gel
35	35	30	0.33	Some residuals on surface
40	35	25	0.33	Cohesive, adhesive gel
45	35	20	0.33	Cohesive, adhesive gel
50	35	15	0.33	Cohesive, adhesive gel
55	35	10	0.33	Cohesive, adhesive gel
60	35	5	0.33	Good gel but dry

Table 4.5 Handling characteristics of hydrogels with increasing ratio monomer:glycerol

Analysis of rheometric behaviour of the hydrogels again shows increasing elastic (G') and viscous (G") responses at high and low frequency stresses with increasing polymer volume fraction. The plasticising effect of glycerol is observed in the reduction of viscoelastic responses of low monomer content hydrogels (high glycerol content) when compared with the equivalent hydrogels studied in 4.5.7.1 that contained a lower concentration of glycerol.

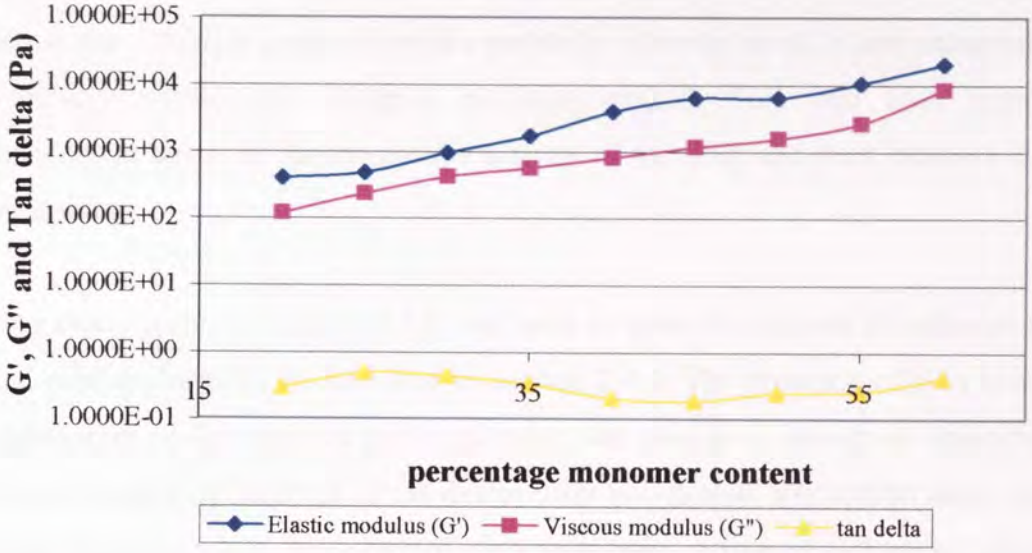


Figure 4.15 Rheological properties (at 1Hz) of 60:40 (SPA:NaAMPS) hydrogels with increasing ratio monomer:glycerol

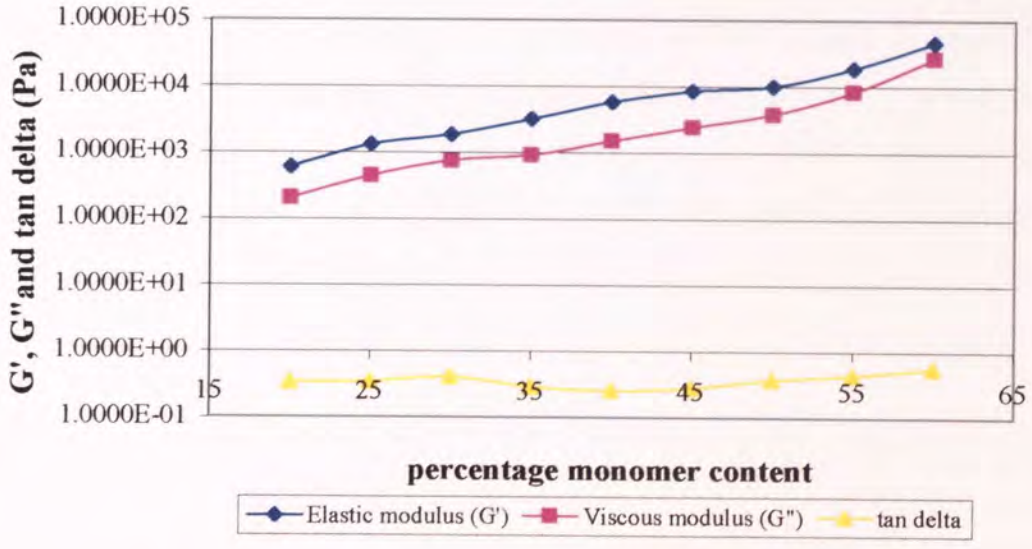


Figure 4.16 Rheological properties (at 10 Hz) of 60:40 (SPA:NaAMPS) hydrogels with increasing monomer:glycerol ratio

4.6 Comparative behaviour of Conventional Medical Tape and Skin Adhesive Hydrogels

Trauma to the skin during removal of an adhesive is an important consideration in the development of adhesive hydrogels for release not only in respect of the associated pain for the patient but because of reduced skin integrity. Damage to the *Stratum Corneum*, the barrier membrane of the skin, will alter transdermal diffusion of solutes at the application site. Multiple applications at a particular site may result in increasing rates of drug delivery should skin integrity be compromised. This will have important consequences in terms of the therapeutic activity of the drug and may induce a risk of toxic poisoning.

Scanning electron microscopy (S.E.M) was used to view the surface of adhesive strips pre- and post-application, as described in section 2.4.4. The presence of skin cells and skin appendages on the samples post-application was used as a measure of the extent of skin trauma caused by removal of the device after one-minute application time. Images of a range of commercially available adhesive tapes were compared to those of a partially hydrated ionic hydrogel. Comparative peel strengths were also determined to aid the comparison (table 4.6).

Material	Figure	Mean peel strength (N/25mm)	Application number (at specific site)
Elastoplast Fabric Strapping	4.17	1.88	0 1
Elastoplast Waterproof Strapping	4.18	0.79	0 1
Boots Micropore Surgical Tape	4.19	0.27	0 1
Zinc Oxide Plaster Tape	4.20	1.09	0 1 2 3
NaAMPS Hydrogel	4.21	3.71	0 1 2 3

Table 4.6 Showing peel strengths of medical adhesive tapes and a standard skin adhesive hydrogel

The peel strengths of the medical adhesive tapes tested ranged from 0.275N/inch to 1.88 N/inch, with the woven fabric and zinc oxide tapes having the higher peel strengths. Peel strength testing of a hydrogel sample of a composition frequently used in the production of skin adhesive hydrogels showed the gel to have a much greater peel strength. This posed the question of the influence of peel strength on physical damage to skin when such adhesives are removed. It was hypothesised that the much greater peel strength of the hydrogel would result in greater physical damage to the skin upon removal of the gel. Preliminary S.E.M. analyses of the five types of skin adhesive were carried out on samples pre- and post-application to a specific test site. Results were used to assess whether this method would allow investigation of the damage caused by application of the adhesives and, if so, the relationship between peel strength and physical damage caused to skin.

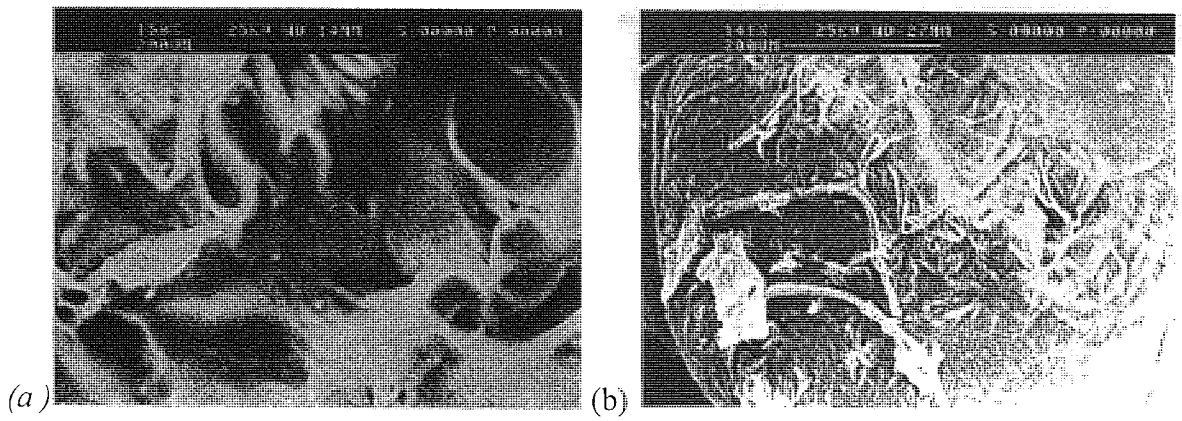


Figure 4.17 S.E.M. image of fabric strapping (a) control (158x200μm), (b) after first peel from application site (141x200μm)

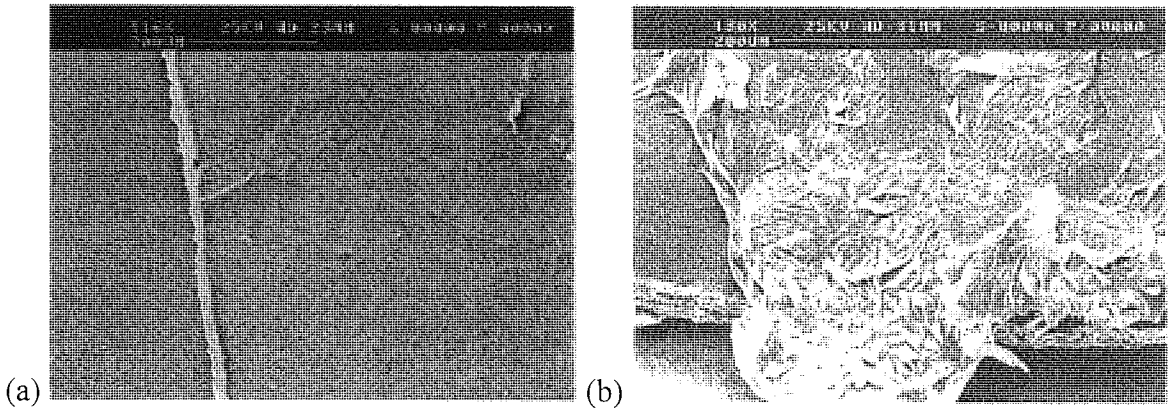


Figure 4.18 S.E.M. image of waterproof strapping: (a) control (116x200μm at 25KV), (b) after first peel from application site (130x200μm at 25KV)

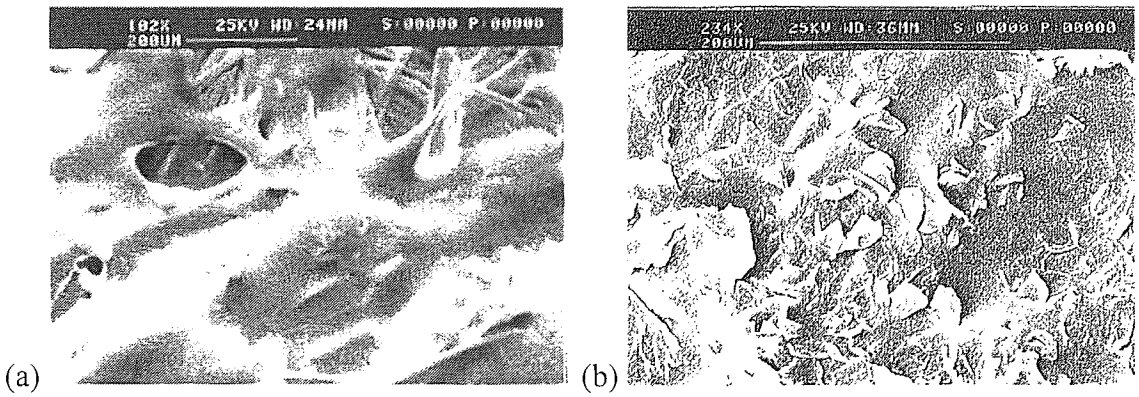


Figure 4.19 S.E.M. image of micropore®: (a) control (102x200μm at 25KV), (b) after first peel at application site (234x200μm at 25KV)

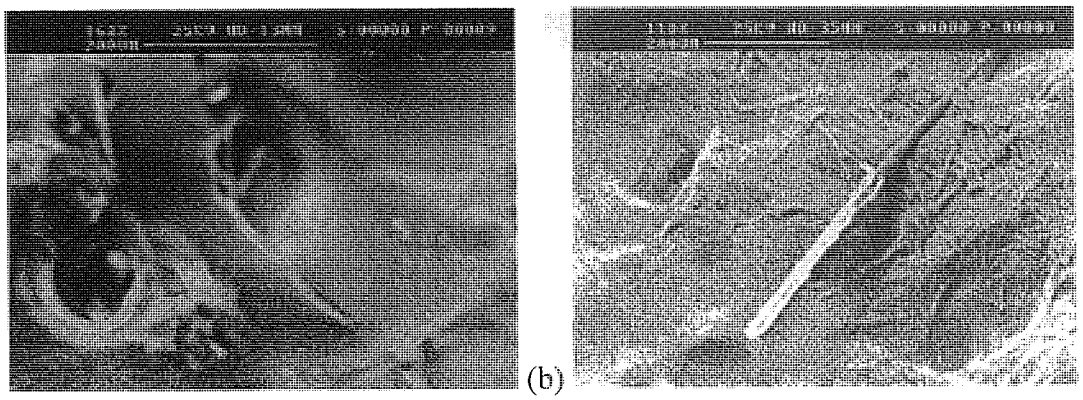


Figure 4.20(i) S.E.M. image of zinc oxide tape: (a) control (162x200μm at 25KV), (b) after first peel at application site (118x200μm at 25KV)

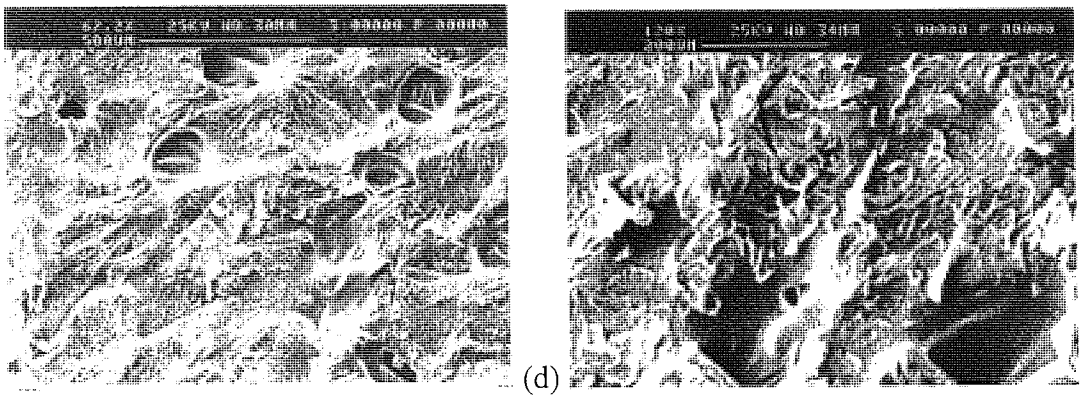


Figure 4.20(ii) S.E.M. image of zinc oxide tape: (c) after second peel at application site (67.2x500μm at 25KV), (d) after third peel at application site (67.2x500μm at 25KV)

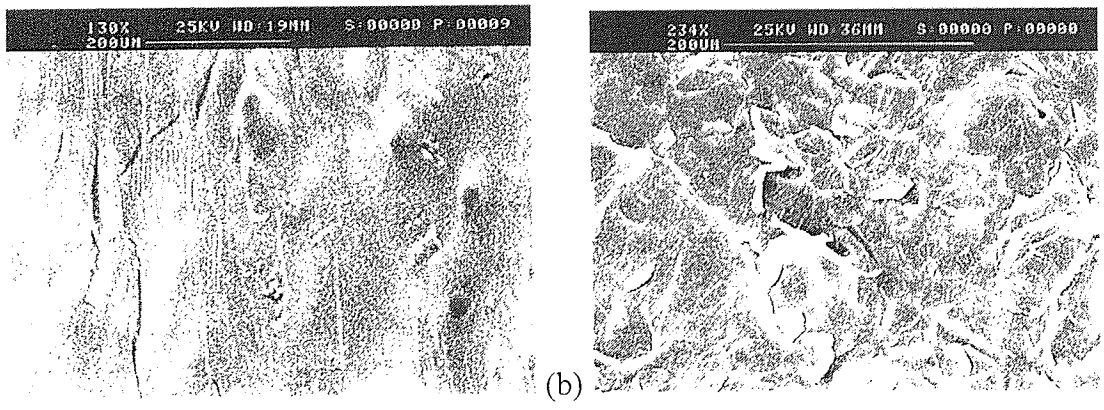
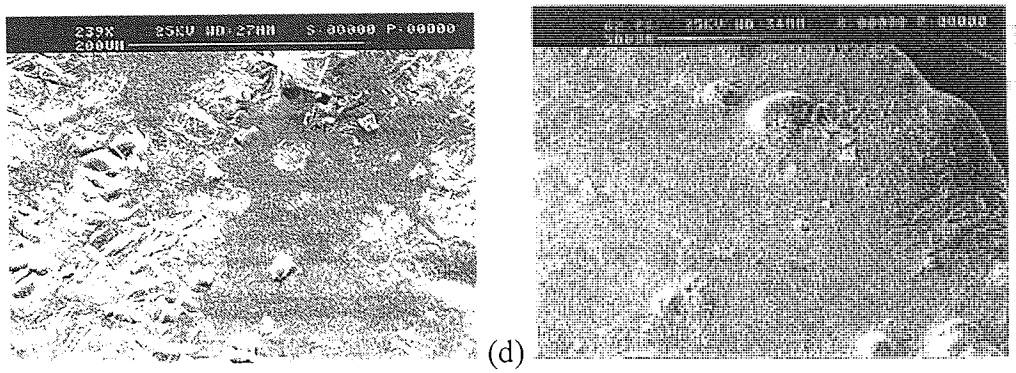


Figure 4.21(i) S.E.M. image of NaAMPs hydrogel: (a) control (130x200μm at 25KV), (b) after first peel at application site (234x200μm at 25KV)



(c) (d)

Figure 4.21(ii) S.E.M. image of NaAMPs hydrogel: (c) after second peel at application site (239x200μm at 25KV), (d) after third peel at application site (62.2x500μm at 25KV)

Images of the control samples of the adhesives show the fabric strapping, micropore, and zinc oxide samples to be porous woven tapes. In contrast, the control samples of the waterproof strapping and the NaAMPs hydrogel both have much smoother surfaces. It is interesting to note that despite them having apparently similar surfaces, the peel strengths of the two materials differ greatly, suggesting that peel strength is not necessarily related to the physical structure of the adhesive but to the mechanisms by which the material acts as an adhesive.

After just one application to the specified site, all of the samples were almost completely covered with skin debris. This debris was in the form of large flakes of skin, which appeared to have been loosely attached dead skin cells on the skin surface that hadn't yet been sloughed off by natural environmental conditions. The samples of fabric strapping and zinc oxide tape, which had the higher peel strengths of the medical adhesive tapes, also had hairs, including the hair follicle, attached, suggesting their peel strengths to be sufficient to remove relatively strongly attached structures and the possibility of damage to living skin cells. Interestingly, the hydrogel sample showed no apparent removal of hairs after one application. This may have been due to either variations in skin structure or the hydrogel being less damaging to the skin.

To assess this possibility and the effect of multiple applications and removals, as would take place in the daily use of such tapes, subsequent peels of zinc oxide tape and hydrogel samples were analysed.

As mentioned, the surface of the zinc oxide control appeared smooth but porous, a consequence of its tightly woven structure. After one application the zinc oxide tape removed skin debris over its entire surface and several hairs, including the hair follicles, suggesting the high peel strength of the tape to be conducive to damage to living cells on the skin surface and to skin structures. Subsequent application of zinc oxide tape to the same site resulted in the removal of yet more skin cells. This time the flakes of skin were much smaller and covered the smooth areas of the sample only. As before, the debris appeared to be that of dead, loose skin. No hairs or other skin structures were seen, suggesting that this second peel simply removed any remaining dead cells from the site.

A third sample of zinc oxide tape applied to the same site removed far fewer flakes of dead skin and instead appeared to have pulled away areas of what had been living skin cells from the site. A greater area of the adhesive tape was clear, but on the more raised areas of the sample a meshwork of "living" skin cells had been transferred to the sample.

For up to two applications the skin adhesive hydrogel sample had a similar appearance to that of the zinc oxide tape after the same procedure. The control hydrogel sample was smooth but with much fewer, smaller pores than the zinc oxide tape. After one application, large flakes of dead skin covered the sample surface, and several fragments of hairs could be seen, but this time the hair follicles had not been removed, despite the greater peel strength of the gel. A second application of the hydrogel to the site removed fewer smaller flakes of dead skin and much of the sample surface remained clear. As with the second peel of zinc oxide tape, no living skin cells appeared to have been removed.

The most interesting result was obtained with the third application of the hydrogel to the site. Unlike the third application of zinc oxide medical tape, this removed almost no skin debris, with most of the sample surface remaining visible. In select areas, small flakes of skin had been removed, but these appeared to be the final remnants of dead skin and debris not removed by previous applications. Such results are promising in terms of the potential for use of skin adhesive hydrogels with relatively high peel strengths compared to their fabric counterparts currently available. The possibility of producing skin adhesive hydrogels with sufficient peel strengths to provide good cohesivity without unnecessary damage to the skin, even after multiple applications, opens up numerous new

applications for the gels. Further analysis of this and other hydrogel compositions by S.E.M. and alternative techniques will dictate the potential of hydrogels for such applications.

4.7 Discussion

The work within this chapter has explored the influence of monomers, crosslinking systems, water and glycerol on the properties of partially hydrated hydrogel systems. Attention has been paid to adhesive and cohesive properties and dynamic mechanical behaviour. These properties are important in determining the suitability of the hydrogel for clinical applications and the ability to manipulate hydrogel behaviour is useful in the development of materials to suit specific skin contact applications. One particular application of interest is the use of hydrogels as topical and transdermal delivery systems. The polymerisation studies were carried out at the beginning of the project, before any specific decision on the types of active compounds that might be investigated for use in delivery systems. For this reason these studies were designed to investigate the possibility of incorporating monomers, into NaAMPS gels, that would influence the release characteristics of gels by modifying their hydrophobic and ionic nature (and thus produce gels with a range of octanol/water partition coefficients, for example). The aim of the investigation was to find, if possible, compositions that would polymerise under the photopolymerisation conditions that are effective for the preparation of NaAMPS gels. There was not an intention to optimise polymerisation conditions for any particular composition.

Both concentration and nature of the crosslinking system used in the production of partially hydrated ionic hydrogels have been shown to play an important role in controlling the rheological and adhesive properties of the gel. An increase in crosslink density within a given system is associated with increased cohesive strength of the hydrogel. This can be achieved either by an increase in the concentration of crosslinker used within the system or by the use of multifunctional crosslinking agents which, in principle, increases effective network density. The difference in behaviour of bifunctional and trifunctional cross-linking agents may be illustrated by reference to results obtained with wholly ionic monomers. The trifunctional cross-linking agent (PETA), and bifunctional cross-linking agent (Ebacryl), when used in SPA:NaAMPS gels at the same concentration gave quite different results. At the concentration used in the baseline studies (section 4.5.3) SPA:NaAMPS gels prepared with bifunctional Ebacryl showed excellent adhesive properties, whereas at the same concentration, SPA:NaAMPS gels prepared with

trifunctional PETA (section 4.5.4, table 4.2) were stiffer and showed poor adhesion. The use of trifunctional cross-linking agents was examined in an attempt to improve the performance of the 50:50 copolymers of ionic and neutral monomers, which, with bifunctional cross-linking agents were much less cohesive than the wholly ionic SPA:NaAMPS system. Although the cohesiveness of the gels increased, and the difference between NaAMPS-based and SPA-based copolymers decreased (a point which will be discussed later), the use of trifunctional cross-linking agents did not overcome the shortcomings of the less effective ionic-neutral copolymer combinations, the reasons for which are more complex.

The effects of monomer composition are a function of several factors. Rate of polymerisation and reactivity ratios of the component monomers will govern the structure of the copolymer whereas their hydrophilicity and possibly solvating potential will affect the function of the copolymer. Although there is no published information on the radical reactivity ratios of these monomers in the concentrated aqueous solutions used in these polymerisations the preliminary studies described in chapter three, together with general principles of monomer structure are of some help. In terms of rate of homopolymerisation in aqueous solution, the ionic monomer NaAMPS, an acrylamide derivative, is expected to be fastest and the ionic acrylate SPA somewhat slower. Although *N,N*-dimethyl acrylamide and *N*-acryloyl morpholine are also acrylamide derivatives, the steric hindrance of the *N*-substituents (disubstitution) has a marked effect in reducing polymerisation rates which are appreciably slower in aqueous solution than those of NaAMPS (monosubstitution) and SPA. *N*-Vinyl pyrrolidone is unusual in that its rate of polymerisation in aqueous solution is appreciably faster than in bulk or organic solution, although still slower than that of the ionic monomers.

Copolymerisation rates appear to be a direct function of homopolymerisation rates, with no unusual cross-reactivity effects. The consequence is that any residual or unpolymerised monomer in the ionic-neutral copolymers described here will be predominantly the neutral monomer. This produces an unusual effect not found in the ionic systems, which are not swollen by or soluble in the constituent monomers. Because the neutral monomers can all act to some degree as solvents for their respective homopolymers, they will have some ability to swell their 50:50 copolymers with ionic monomers. It is probable that this effect contributes to the fact that some of these

copolymers are less coherent and "leggier" than the wholly ionic gels. It may well be that the difference between the 50:50 copolymers is more related to residual monomer and solvent effects than to the structure of the polymeric component. This does suggest, however that by optimising polymerisation conditions and reducing the proportion of neutral monomer a range of very effective skin adhesive gels would be produced.

The one remaining point for comment is the observed difference between NaAMPS copolymers and SPA copolymers, which became insignificant when the trifunctional cross-linking agent, PETA, was used. This is undoubtedly a function of the greater scope for interchain bonding between the pendant NaAMPS groups which contain both amide and sulphonate groups. The amide-sulphonate interaction produces greater interchain cohesion. A similar effect is seen in the mechanical properties of SPA:NaAMPS copolymers in which the ratio of the two monomers is varied (figures 4.11 and 4.12). These go through a gentle maximum at around 30% SPA consistent with the enhancement of sulphonate-amide interchain links by increasing the availability of sulphonate groups.

Chapter Five

Hydrogels for ocular and dermal delivery: Model compound studies

5. Hydrogels for ocular and dermal delivery: model compound studies

5.1 Hydrogels for drug release

The ease with which molecules can be loaded into and diffuse out of hydrogels makes them an obvious consideration as vehicles for drug delivery, however this ease of movement of molecules through the hydrogel network has led to some speculation regarding problems with control of release. Specifically, it has previously been assumed that loaded compounds are simply dumped from the aqueous phase of a hydrogel into an aqueous external environment (Centre for Professional Advancement; Skin Product Development, 2000). As hydrogels are simply water swollen polymer networks they are frequently assumed by those unfamiliar with synthetic hydrogel production to be almost identical in their physical and chemical characteristics. In fact, hydrogel composition and resultant properties can be manipulated to produce a broad range of materials with application-specific properties. Alteration of the polymer backbone of a hydrogel can be used to tailor both mechanical and surface properties. This phenomenon might also be used to alter the affinity of the hydrogel for a particular compound, and as a result allow some degree of control over the release of the compound from the gel. Indeed, modified hydrogels have previously been successfully employed as controlled-release implant devices in a number of applications (Gupta, 2002) and the rapid diffusion of some molecules through hydrogel delivery vehicles has been shown to provide high transdermal delivery rates even in the absence of penetration enhancers (Feldstein, 1996).

It would seem likely that, through manipulation of hydrogel composition, there is potential for the release characteristics of the material to be modified extensively so that a defined dose of a particular drug can be loaded into the hydrogel and released at a previously established rate and time, to a specific biological site. Such modification requires the identification of the release controlling characteristics of both the hydrogel material and the drug molecule. This programme of work will examine the release characteristics of hydrogels for dermal and ocular release applications. Hydrogel membranes and contact lens forms frequently used in such applications will be studied, as opposed to the hydrogel spheres employed in parenteral release applications that are

more commonly used in the characterisation of release profiles. It is important that these studies are representative of release from a single surface onto ocular and dermal sites in contrast to the 3-dimensional release seen in parenteral release devices. Release controlling factors relating to hydrogel composition and characteristics, release compound and the nature of the external release environment will be considered in the studies, with the aim of establishing the degree and nature of the influence these factors have on release and whether release from these hydrogel forms can indeed be controlled.

Release from conventional dosage forms such as tablets occurs much faster than absorption of the drug across cell membranes and as such absorption is the rate limiting step of drug delivery. Conversely, release rate from controlled release devices is the rate-limiting step and as such the absorptive phase of drug delivery kinetics becomes insignificant compared to the drug release phase being manipulated (Wai-Yip Lee & Robinson, 2003). Ideally then, a controlled release device will supply a drug at a constant rate equal to its rate of absorption or elimination from the delivery site independent of the amount of drug remaining in the delivery device. This is known as zero-order release kinetics. In the development of hydrogels for controlled release, the ability to produce a material possessing zero-order release characteristics is the ultimate goal of the design process.

5.2 Permeability of a solute through a hydrogel - ionisation, partition, and distribution of a compound.

It is known that release of a drug from a hydrogel is determined by its permeation through the polymer to the release surface. This is in turn dependent on the nature of both the hydrogel and the external environment, and the form of the compound being released. Permeation can be defined as a product of the diffusion co-efficient (a transport property) and the partition co-efficient (a thermodynamic property) and as such these are important controlling factors of release. This is demonstrated most familiarly in the oxygen permeability of hydrogel contact lenses, DK, where D= diffusion and K= partition (or solubility) of the oxygen species within the polymer network. By understanding how a hydrogel network alters the transport and thermodynamic properties of a system, permeation of a drug through a hydrogel to a delivery site can be manipulated to suit a particular application.

5.2.1 Diffusion through a hydrogel

A commonly used expression for permeation and transport of a species across a membrane is:

$$P = d \times s$$

Where; P = permeation
d = diffusion*
s = solubility

In looking at the release and transport phenomenon of drugs and model release compounds, the three important parameters affecting permeability are ionisation of the drug, partition co-efficients, and distribution co-efficient. These will each be dealt with separately within this chapter.

- Unfortunately, in drug delivery studies "d" is conveniently used to represent "distribution co-efficient" and so care must be taken to avoid confusion with its use to represent "diffusion".

When a monolithic diffusion-controlled hydrogel device comes into contact with an external medium, drug molecules dissolved in the matrix will diffuse across the device-medium interface until the chemical potential of the solute is equal in both the bulk solution and the polymer phase. The portion of drug most readily available for release is that adjacent to the surface of the gel. As drug molecules diffuse out from the hydrogel surface into the external medium the zone just inside the device becomes depleted of solid drug and a concentration gradient of the dissolved drug is established across the zone. Drug molecules will diffuse through the device to regain chemical equilibrium. The flux of drug molecules in this way is determined by the diffusion co-efficient, D_I; the proportionality constant between flux, j_i, and the concentration gradient of the solute, as defined by Fick's first law (equation 5.1) (Gehrke et al, 1997).

Fick's first law $$j_i = -D_i\left(\frac{dC_i}{dz}\right)$$ Equation 5.1

Where j_i = flux of solute i (mol/cm^2)

D_i = diffusion co-efficient of solute i (cm^2/s)

dC_i/d_z = concentration gradient

The equation for steady state flux, j_i, of a solute, i, across a membrane from a donor phase to a receptor phase is expressed as;

$$j_i = \frac{K_i D_i}{L}(C_{di} - C_{ri}) \quad \text{or} \quad j_i = \frac{P_i}{L}(C_{di} - C_{ri})$$ Equation 5.2

Where;j_i = flux of solute, i (mol/cm^2)

C_{di} = concentration of solute, i, in donor phase (mol/cm^3)

C_{ri} = concentration of solute, i, in receptor phase (mol/cm^3)

D_i = diffusion co-efficient of solute, i (cm^2/s)

K_i = partition co-efficient of solute

P_i = permeability of solute, i (cm^2/s) = K_iD_i

L = membrane thickness (cm)

5.2.2 Distribution and partition co-efficients

Partitioning of a solute between a hydrogel and the external environment to achieve its chemical potential is dependent on the chemical and physical properties of both the solute and the hydrogel. The distribution of a compound is dependent on several interactions including electrical potential, hydrophobicity, biospecific affinity and conformational effects, which together determine the overall partition co-efficient (Gehrke et al, 1997).

Distribution co-efficients are a generalised term used to indicate the distribution of both ionised and non-ionised forms of a solute between an aqueous and an organic phase. They give information about the pharmacokinetic affinity of a molecule for lipoidal and aqueous environments at different pH. These values can be used to predict the distribution of a molecule between the aqueous phase and polymer phase of a hydrogel, and its release from the hydrogel into the lipoidal and aqueous components of the biological interface.

$$D_{\,distribution\ co-efficient} = \frac{[unionised + ionised\ species]\,oct}{[unionised + ionised\ species]\,water}$$

Water-octanol partition coefficients, expressed as log K_{ow}, reflect the ability of unionised species of a compound to partition between an aqueous phase and an immiscible organic phase (usually 1-octanol). Values of log K_{ow} between 0 and -1 mean that the marker molecules are comparably soluble in both the octanol and the water, larger negative values indicate a greater affinity for the aqueous phase.

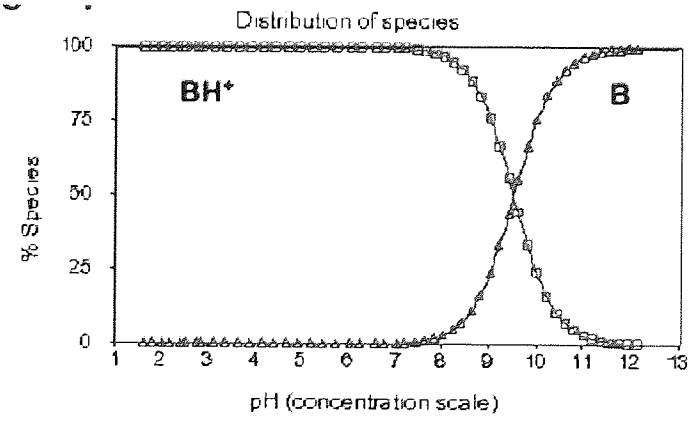
$$P_{\,partition\ co-efficient} = \frac{[unionisedspecies]oct}{[unionisedspecies]water}$$

5.2.3 Ionisation of a compound

The degree of ionisation of a compound has a marked effect on the ability of the compound to partition between two phases. When acidic/basic compounds are subjected to varying pH they undergo changes from unionised to ionised forms. Figures 5.1 and 5.2 depict the change in distribution of species (ionised and unionised) with change in pH of a typical acid and a typical base. The distribution of a compound between its ionised and non-ionised forms at different pH values is indicated by its pKa. When the pH of the solution is equal to the pKa of a compound within the solution, concentrations of dissociated and undissociated species are equal.

$$pKa = pH + \log_{10} \frac{conjugated\ acid}{conjugated\ base}$$

pKa is a measure of the tendency of a molecule or ion to keep a proton, H^+, at its ionisation centre with change in pH; the greater this tendency, the lower the degree of ionisation of the compound. As it is the ionised form of a drug that will partition between the delivery vehicle and receptor site, the pH of both delivery vehicle and receptor site affect potential dosage levels. The partition co-efficient of the ionised drug and the hydrophilicity of the receptor site control the distribution of the drug and consequently its bioavailability.



$$BH^+ \rightleftharpoons H^+ + B$$

Conjugate acid **Base**

Figure 5.1 Distribution of species (ionised/unionised) for a typical base with change in pH

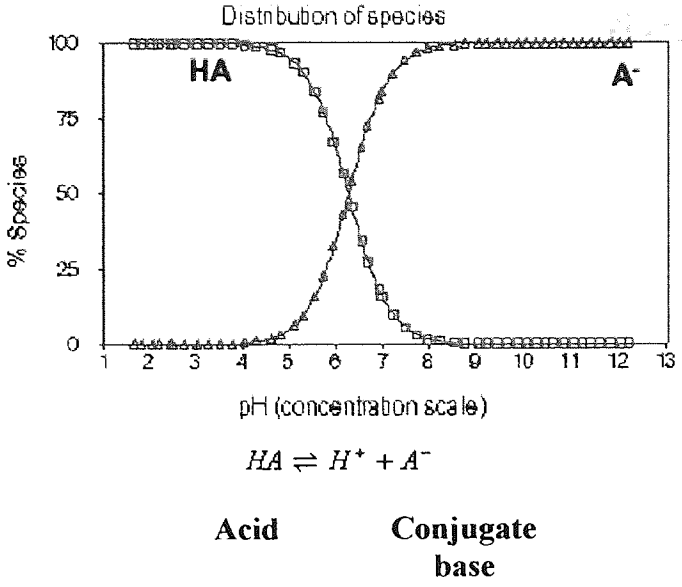


Figure 5.2 Distribution of species (ionised/unionised) for a typical acid with change in pH

The way in which an active component is partitioned within a hydrogel is the key issue that controls subsequent release behaviour. Because many drugs are ionic in nature, and capable of existing in both ionised and non-ionised forms, the pH of the aqueous component of the hydrogel and the pKa of the drug will lead to an equilibrium distribution independent of the form in which the drug is introduced.

Figure 5.3 shows the distribution co-efficients of several drugs that have the same distribution co-efficient at pH7.4. The wide variation in distribution co-efficients of the drugs over physiological pH demonstrates the importance of both pKa of a compound and the pH of its environment in affecting ionisation of the compound and subsequently its partitioning within a delivery system.

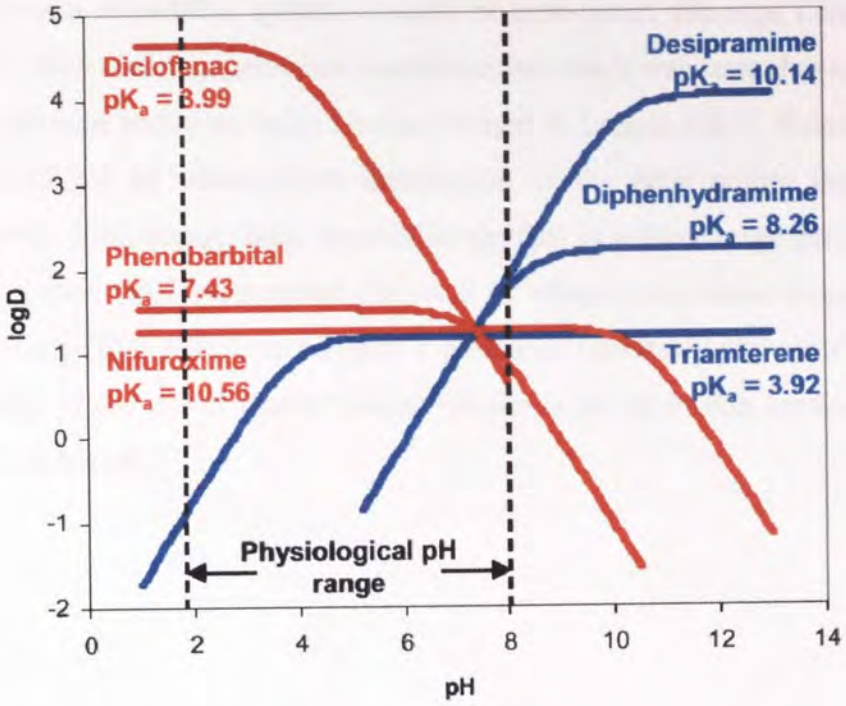


Figure 5.3 Change in distribution coefficient with pH of several drugs which have the same distribution coefficient at pH 7.4

The octanol/water partition coefficients (or distribution coefficients for the ionised form of the drug) will govern the release pathways of the drug from polymeric and aqueous hydrogel components into lipoidal and aqueous components of the environment.

5.2.4 Release profiles

If we consider a solute to be homogeneously dissolved within the hydrogel matrix and one planar surface is available for release, the amount of solute delivered can be calculated by solving Fick's second law of diffusion (equation 5.3) (Hadgraft & Guy, 1987)

Fick's second law of diffusion $$\frac{dC}{dt} = D\left(\frac{d^2C}{dx^2}\right)$$ Equation 5.3

Drug release from a monolithic system is rarely of zero-order, although Langer (1980) created a device with complex geometric modifications which was later shown to release bovine serum albumin with zero-order kinetics (Siegel & Langer,1983). Release profiles can also be modified by non-uniform distribution of the drug within the polymer. Usually, however, drug release from monolithic devices is a three stage process which begins with an initial rapid burst period followed by release as a linear function of the square root of time (first order), and finally a period of infinitesimally slow release. It will be important to see if this type of release profile is found in thin section hydrogel sheets and contact lenses.

5.3 Controlling release

The factors that control the solubility, diffusion, and subsequent release of a drug from a hydrogel can be divided into three main categories as follows:

- Those relating to the drug being released (e.g. load concentration, molecular size, water/octanol partition co-efficient and polarity).
- Those relating to the hydrogel delivery vehicle (e.g. Equilibrium Water Content and degree of hydration, polarity, and chemical composition).
- Those relating to the external release environment (e.g. pH, aqueous/organic nature), and more specifically, how this differs from the environment within the hydrogel.

The relationships between drug properties and release from hydrogels that have been described in this chapter can be used to anticipate the release characteristics of a specific drug/hydrogel delivery vehicle combination in particular release conditions. Regulation of these release conditions can be used to promote the desired release behaviour for a particular drug. In many cases drug characteristics and external environmental conditions are predetermined and immutable however the physical and chemical characteristics of the delivery vehicle can be altered. By manipulating hydrogel properties the delivery vehicle can be tailored to provide delivery conditions which will give a release profile suited to a specific application.

It has been demonstrated, both theoretically and experimentally, that solute diffusion in water-swollen hydrogels occurs mainly through the water filled pores of the hydrogel matrix. Solutes are dispersed or dissolved in the free water fraction of the water that is held within the pores of the hydrogel and diffuse through the hydrogel network within a shell of this unbound water. As such the amount of water within a hydrogel material (volume fraction) and the state of this water strongly affects potential diffusion rates.

The total amount of water held within a fully hydrated hydrogel; its equilibrium water content, depends on the chemical structure of the hydrogel, both in terms of the hydrophilicity of the polymer and space available for the water. The hydrophilicity of the polymer can be influenced by co-polymerisation of hydrophilic and hydrophobic

component monomers at varying ratios. These monomers can also be used as a means of introducing a polar component to the material. The presence of a polar component being important in its influence on the loading and release of ionic compounds. The effect of a predominant polar component on the affinity of hydrogels for anionic compounds and their resulting release profiles is examined in chapter six of this thesis.

The crosslink density of a hydrogel governs its mechanical strength and is important for maintaining the integrity of a hydrogel release vehicle throughout its lifetime. Alteration of crosslink density can be used to achieve the desired mechanical properties of a hydrogel; in the case of release vehicles for dermal applications this is ideally a relatively strong yet elastic material. An increase in crosslink density to improve the mechanical strength of a hydrogel will also affect diffusion and release of any drug within the hydrogel. The crosslink density of a hydrogel, and more specifically the average molecular weight of polymer chains between neighbouring crosslinks, determines the flexibility of the polymer chains and accompanying ability of the hydrogel to swell with water (fluid). Chains with greater flexibility confer reduced elastic network refraction forces and so accommodate higher levels of free water. As described previously, this has a strong influence on rates of diffusion of a solute through the hydrogel. The mesh size (ξ) of a hydrogel, a correlation of the distance between adjacent crosslinks, gives a measure of the mean space available between the polymer chains for diffusion of drug molecules held within the free water. Even in the presence of sufficient free water for the dissolution of a drug, high molecular weight compounds can be expected to show very slow release kinetics due to the limitations imposed by the reduced mesh size of highly cross-linked hydrogels.

The effect of degree of hydration of a hydrogel on loading and release of a compound must also be considered. Partial hydration of a hydrogel below its equilibrium water content reduces the amount of free water available for dissolution or dispersion of release compounds also affecting diffusion rates of loaded compounds.

Each of these parameters can be measured and used to hypothesise release behaviour of a hydrogel, by theoretical models or through a variety of experimental techniques. Although some methods of measurement are vulnerable to subjectivity they provide

useful guidelines as to the acceptable range of values within which the hydrogel will be suitable for an intended application.

5.4 Drug loading

A number of techniques are available for loading and immobilising drugs within hydrogels. Each has it's own advantages and disadvantages that determine which method is best suited to a particular application. The techniques can be divided into four main types; physical entrapment, electrostatic attraction, physical adsorption and chemical bonding. Of these, physical entrapment of the solute within the hydrogel network structure is the easiest and simplest approach and the one chosen for this work.

A solute can be physically entrapped in a hydrogel during polymerisation or imbibed into a pre-prepared hydrogel as a solution. Polymerisation in the presence of the solute traps the solute until the hydrogel is placed in an environment that causes it to swell. This increases the mesh size of the hydrogel (ξ) allowing the solute to diffuse out. Use of high concentrations of crosslinker may reduce mesh size to the extent of preventing solute diffusion. It is important to ensure that the solute will not react with the monomers in the system and that polymerisation is not detrimental to therapeutic activity. For this reason, photopolymerisation is often chosen in preference to thermal polymerisation of these materials where possible. Loading of a solute by placing a pre-prepared hydrogel in a drug solution for an extended period avoids these issues, but care must be taken to ensure that crosslink density is sufficient to trap the solute within the hydrogel. This approach is unsuitable for loading of partially hydrated skin adhesive hydrogels because of the swelling and associated alteration in degree of hydration of the hydrogel.

5.5 Aims of this chapter

Much of the literature concerning drug loading and release from hydrogels looks at the release of a particular drug and the adaptation of the hydrogel vehicle to suit the intended pharmaceutical application accordingly. Few studies investigate the broader potential of manipulation of hydrogel composition and corresponding release characteristics and their relation to the chemical properties of drug molecules. This work is concerned with the ways in which hydrogel systems can be manipulated in order to modulate and control release profiles of a range of active species. That is, an attempt to investigate the underlying principles and patterns of release behaviour in hydrogel release system rather than the design of a release system for a specific active. Experimental work examined the significance within hydrogel release systems of some factors demonstrated by others to influence diffusion and release of loaded compounds from release devices and whether these factors have a similar role in topical hydrogel release systems and could therefore be employed in the design of topical hydrogel release systems for controlled release.

A great deal of effective work in establishing release characteristics of hydrogels can be carried out using model compounds in place of specific drugs. These allow trends across categories of active characteristics to be studied and are easier to analyse than drugs themselves e.g. colorimetrically. Useful information can be gained from the extensive range of variations in specific characteristics of the model compounds, e.g. molecular weight, acidity, the presence of functional groups, hydrophobicity.

Experimental work in this chapter focussed on the release vehicle rather than being drug-related and assessed diffusion of the model compound to the surface of the hydrogel: available for topical or transdermal administration. Although time has been spent optimising skin adhesive hydrogel properties and compositions, initial release work was carried out on fully hydrated compositions in sheet and contact lens form as this allowed elimination of issues associated with swell of the hydrogel by imbibition of release medium. Identical monomer compositions in partially hydrated forms and partially hydrated modified compositions of equivalent equilibrium water content to these materials can be produced in the form of adhesive hydrogels. Rather than a systemic study of all material variables, representative hydrogel structures from the fully hydrated,

substantially neutral, class of materials of the sort used in contact lenses were selected to provide information about the effects of both polymeric structure and hydrogel water content on release. A range of easily monitored compounds was chosen, as models of low molecular weight drugs or pharmaceutically active compounds, for the release experiments. As has been observed for other release devices, the molecular size, charge (acidity or basicity) and hydrophobicity of the compounds were anticipated to be important in release. Together with partition (log P) and diffusion co-efficients (log D) of non-ionised and ionised forms of a compound respectively, the study of their effect on release behaviour is hoped to provide pH-dependent profiles of release from neutral hydrogel materials into both hydrophilic and lipophilic media.

It is a widely held belief, which was voiced at The Centre for Professional Advancement's course on Skin Product Development attended by the researcher in 2000, that hydrogels simply dump loaded compounds at rates too high to be of medical use. From this work is it hoped that some "real challenge" molecules can be examined to test this hypothesis and establish whether it is possible, by manipulation of the polymer structure and degree of hydration of the gel, to control release from hydrogels in planar sheet form.

5.6 Release of model compounds

5.6.1 Use of dye models

Research into the loading and release of specific drugs from novel delivery vehicles can be expensive and wasteful, especially during the preliminary stages of delivery material development. The use of appropriate model compounds as marker molecules provides an inexpensive and simple-to-use alternative for assessing loading and release behaviour from hydrogels in relation to the chemical characteristics of a compound. One convenient method of measuring release of a compound is by spectrophotometry; the concentrations of a dye released from a hydrogel into a chosen release medium can easily be calculated using colorimetric measurements.

A wide variety of dyes of various molecular weights and chemical characteristics are available and can be used as models for drugs with similar properties to give indications of how the drugs themselves are likely to behave under different release conditions. This information can be used in the modification of the hydrogel composition to suit a specific application.

The molecular weight of a compound was considered a key parameter in the study of hydrogel release systems, in consideration of the effects of crosslink density on the mesh size of hydrogels. It is important to reconcile the ability of a solute to diffuse through the hydrogel with the mechanical endurance of the hydrogel itself. For this reason, model compounds of low molecular weight drugs were chosen.

The hydrophilicity of hydrogels lends them to the loading of hydrophilic molecules in particular. Partition of a loaded drug between the hydrogel and the external environment will play a key part in the bioavailability of the drug. Water/octanol partition co-efficients ($K_{o/w}$) were used as an indicator of the relative hydrophilicity of the model compounds used. Model compounds with negative and positive water/octanol partition co-efficients were included in the study so that extent of the influence of hydrophilicity on partition of the model compounds into both aqueous and organic media could be investigated.

Table 5.1 shows the structure and chemical characteristics of each of the model compounds used. The suitability of these model compounds for loading and measurement post-release was assessed to confirm their practical use in experimental profiling of release from hydrogels. All of the compound/medium combinations proved suitable with the exception of fluorescein in octanol. Absence of colour in this combination excluded it from the study.

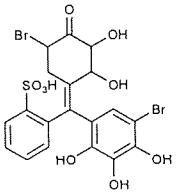
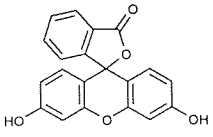
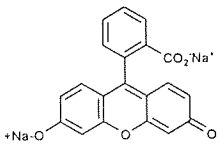
Dye Model	Structure	MW	pKa	$K_{o/w}$ (log P)	Absorbance (λ)
Bromopyrogallol red		558.2	–	4.32	552nm
Fluorescein		332.3	6.4	3.35	490nm (514nm @ pH 8.0)
Fluorescein sodium salt		376.3	6.4	-0.67	491nm

Table 5.1 Chemical characteristics of model compounds

Release into both aqueous and organic media was studied. Aqueous media were buffered in order that the release compound could not influence the pH and ionisation of the external environment.

Interactions between the model compound and the aqueous and polymeric components of the hydrogel and the external release medium will govern partitioning of the model compound between these phases. The physiochemical properties of the model compound, hydrogel and release media will influence interactions at each of the different stages involved in release from hydrogels and determine the release profile of a particular compound from a hydrogel composition into a chosen release medium.

There is potential for the aqueous media to diffuse into the hydrogel and change the pH of the environment within the hydrogel. This presents potential for change in the ionisation of the compound loaded into the hydrogel depending on its pKa. Different partition co-efficients of the ionised and unionised forms of a drug will subsequently determine partition of the compound into the medium.

The polymer network and the aqueous portion of the hydrogel can be considered to be in competition, with extent of this competition depending on the nature of the polymer, which is further dependent on the monomers incorporated in the material. The polymer network, being the more hydrophobic portion of the hydrogel, will be the favoured environment for non-ionised species that have positive partition co-efficients (hydrophobic tendencies) for example fluorescein. Hydrophobic interaction between these species and the polymer backbone will influence maximum loading capacities of the hydrogel, impede release rates and limit dosage levels. Likewise, the aqueous component of the hydrogel will be the favoured environment for ionised species that have negative partition co-efficients (hydrophilic tendencies) for example sodium fluorescein.

The water-octanol partition co-efficients of the ionised and non-ionised components of a drug govern their release from a hydrogel into the lipoidal and aqueous components of the biological interface. Charge/polar interactions and acid-base interactions between the polymeric component of the hydrogel and release compounds will differ with the ionicity and hydrophilicity of the compound, affecting the freedom of molecules to diffuse out of the hydrogel into the external medium. Acidic fluorescein for example, is likely to interact very favourably with lipophilic polymer chains.

5.6.2 Calibration curves

Calibration curves were constructed for the model compounds so that the measured absorbencies of release samples could be compared against the curves and concentrations of the released model compounds could be calculated. By measuring release at regular intervals over an extended time period, release rates and proportions can be profiled.

Serial dilutions (1 in 2) were made from 0.1% stock solutions of the model compounds in both aqueous (phosphate buffered saline pH7, aqueous buffer pH4) and organic (octanol) solvents. Samples from each dilution were measured in cuvettes on a Cecil CE404 colorimeter, using uncontaminated solvent as controls. The UV spectrum for each of the dyes was used to decide which colorimetric filter would provide the broadest measurement range for that dye (see figure 5.4). Filters used for each dye/solvent combination are noted on the calibration curves. Measured absorbance values were plotted against the known concentrations of each sample to produce calibration curves.

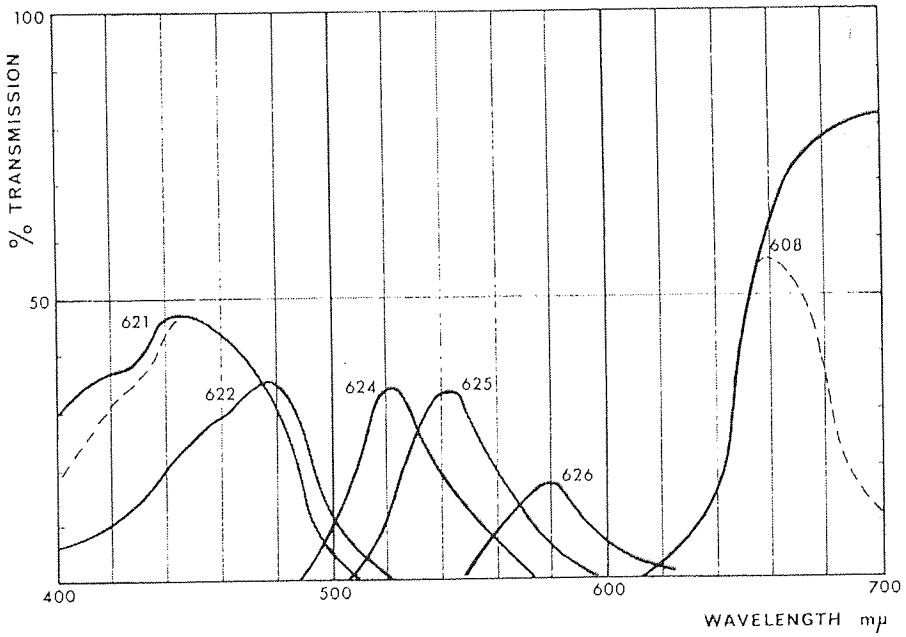


Figure 5.4. Wavelength range of colorimetric filters

Calibration curves for each of the model compounds used in experiments are shown for octanol, phosphate buffered saline and pH4 aqueous buffer. Polynomial equations are given for each curve along with respective values for R^2; a statistical measure of how well a regression line approximates real data points. An R^2 value of 1 (100%) indicates a perfect fit.

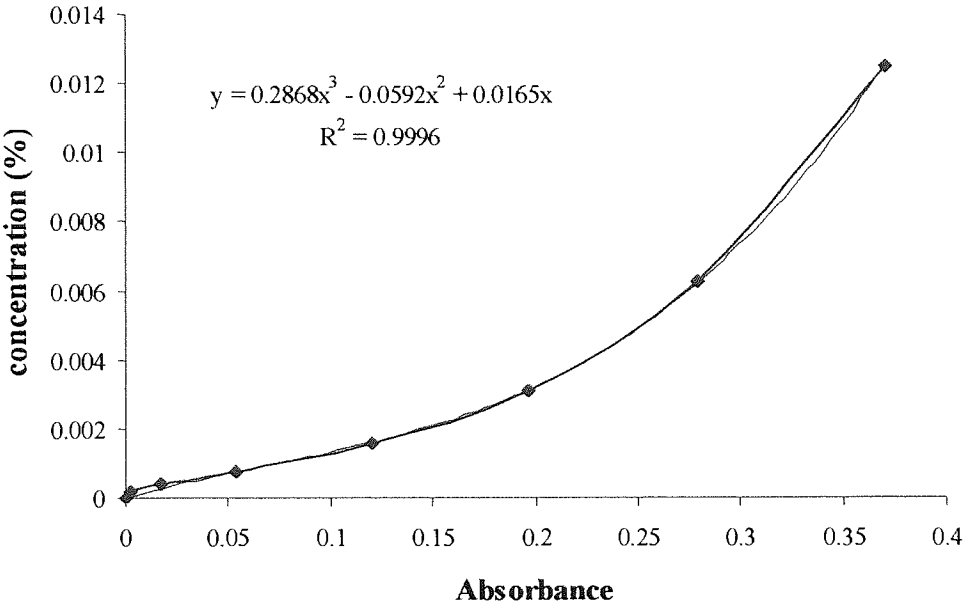


Figure 5.5 Calibration curve for bromopyrogallol red in phosphate buffered saline measured at 626mμ.

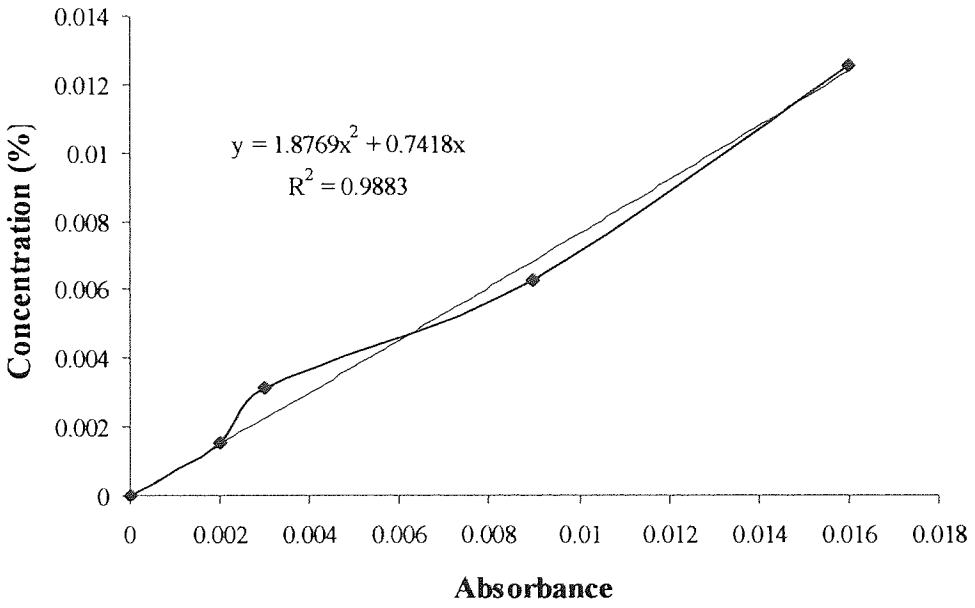


Figure 5.6 Calibration curve for fluorescein in phosphate buffered saline measured at 624mμ.

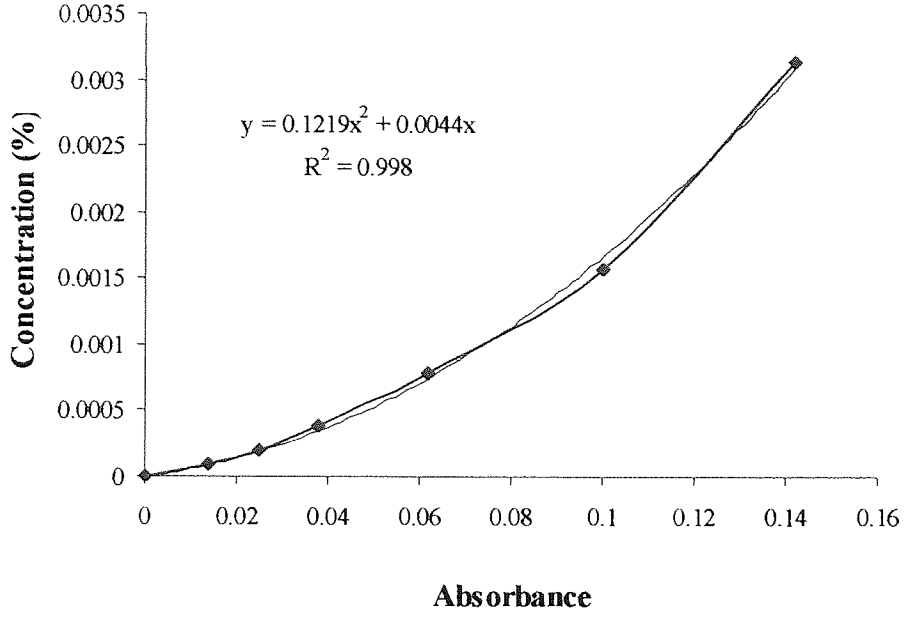


Figure 5.7 Calibration curve for fluorescein in pH4 buffer measured at 624mμ.

Dilution of fluorescein in octanol gave inconsistent colorimetric measurements; in many cases samples were almost colourless. For this reason an accurate calibration curve could not be plotted for fluorescein in octanol.

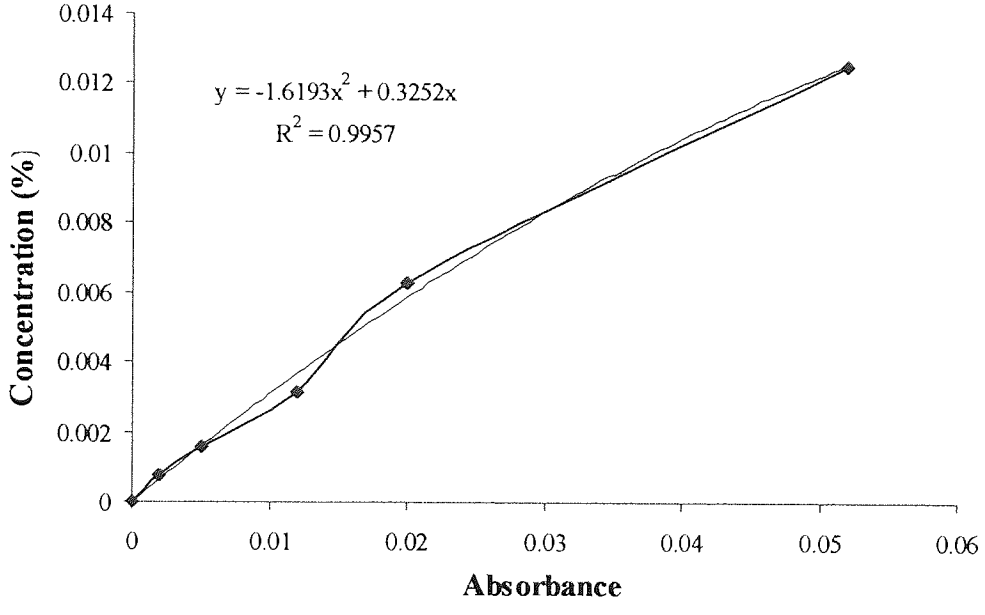


Figure 5.8 Calibration curve for sodium fluorescein in phosphate buffered saline measured at 624mμ.

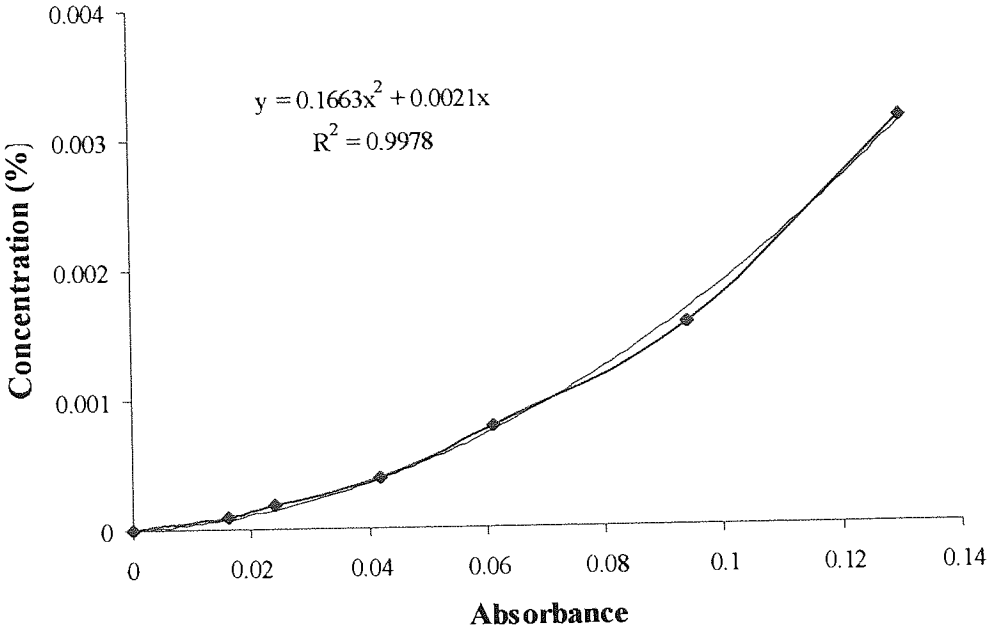


Figure 5.9 Calibration curve for sodium fluorescein in pH4 buffer measured at 624mμ.

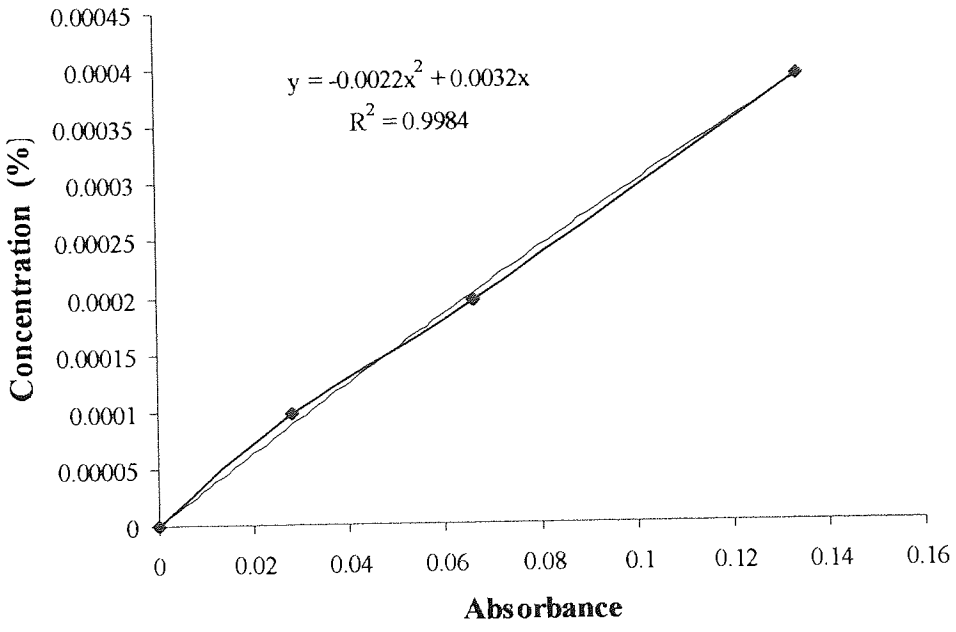


Figure 5.10 Calibration curve for sodium fluorescein in octanol measured at 624mμ.

5.6.3 Imbibition of model dyes into fully-hydrated neutral hydrogels

In order to fully exploit the potential of hydrogel contact lenses and skin adhesive hydrogel sheets for ocular and dermal drug delivery it is necessary to first determine the ability of the hydrogels to absorb and desorb solutes. Investigation of the effects of hydrogel composition in directing and controlling release under different release conditions can be used to develop efficient application-specific materials.

The effects seen at each of the different stages of drug delivery from a hydrogel were illustrated by the study of the release of model compounds from representative hydrogel structures from the class of fully hydrated, neutral hydrogels. Two types of commercially available contact lens and two fully-hydrated hydrogel membranes of differing equilibrium water content and hydrophilicity were used to investigate the effects and relative importance of delivery vehicle characteristics on solute release.

The hydrogel samples, detailed in table 5.2, were loaded with model compounds by imbibition. Loading of fully hydrated hydrogels in this way represents the method most likely to be used in commercial production of fully hydrated devices such as therapeutic contact lenses. The relatively small population of potential users of these devices makes it logically unreasonable to expect manufacturers to devote part of their mass production process to loading drugs into the lenses during production. Loading of the drug into the finished article presents a more feasible approach.

Hydrogel composition	Hydrogel form	Water content (%)
HEMA	Contact lens	38
MMA:NVP	Contact lens	67
HEMA:AMO (80:20)	Membrane	45
HEMA:NVP (80:20)	Membrane	45

Table 5.2 Water contents of hydrogels used in this study.

The hydrogels were loaded with either fluorescein (non-ionised) or the sodium salt of fluorescein (ionised) or bromopyrogallol red. These model compounds were used to study of the effect of both ionisation and water-octanol partition co-efficient ($K_{o/w}$) of a molecule on its release from the different hydrogels. Release into both organic and aqueous media demonstrated the effects of hydrophilicity of the external environment in relation to the partition co-efficient of the loaded compound. Use of aqueous release media at pH4 and pH7 (above and below the pKa of fluorescein) show the effect of pH of delivery site on the ionisation of a release compound and consequently its release.

The water within the contact lenses was replaced with Methanol (MeOH) which acts as a bridging solvent to aid imbibition of dyes into the hydrogels. The lenses were rinsed with distilled water to wash away storage solution salts, blotted on filter paper and dehydrated in a desiccator until all water had been removed (20 hours). They were then rehydrated in MeOH overnight at room temperature. The liquid portion of saturated solutions of MeOH and each model compound were used to load the hydrogels. The loaded hydrogels were stored in the near-saturated solution until time of use to avoid partitioning of the dyes out of the gels during storage. Prior to release measurements, the samples were equilibrated in distilled water to their original size as a means of minimising variations in hydration of the samples. This also removed any excess unbound dye from the hydrogel surface.

Excess water was blotted onto filter paper and the samples were dried in air for 10 minutes to ensure excess surface moisture had evaporated and to minimise lens to lens variations in free water content.

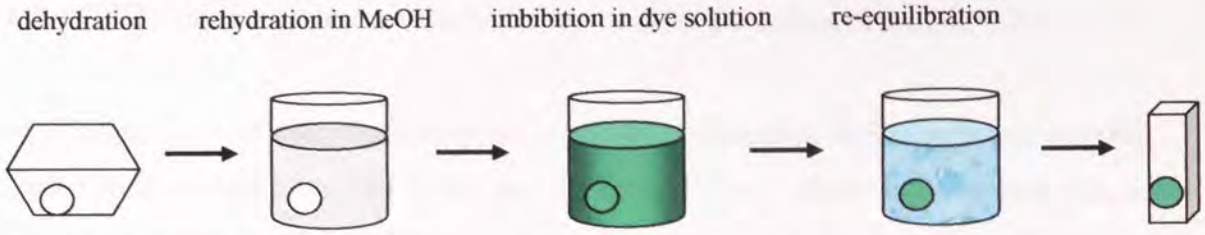


Figure 5.11 Schematic diagram of the steps involved in loading a fully-hydrated hydrogel by imbibition.

5.6.4 Measuring release

Release of the model compounds from fully hydrated hydrogels that had been loaded according to the method described in section 5.6.3 was monitored by measurement of the absorbance of the release media over time. Measured absorbencies were converted into concentrations using the polynomial equations plotted for the calibration curves of each of the model compounds. These are shown along with values for R^2 on each of the calibration curves (section 5.6.2). The calibration curve used to calculate concentrations in samples was that for the form in which the model compound would be released under the specified experimental conditions and is noted in figure captions. Release was then plotted as cumulative concentration values to give a systematic basis for comparison of release profiles. The results gave workable release profiles for the loaded compounds confirming the suitability of this technique for assessment of dye release from fully hydrated hydrogels.

Maintenance of sink conditions during experimental measurement of release is important in ensuring that the release profile of a system is not limited by the solubility of the release agent in the receptor medium and as such that experimental release kinetics are accurate and quantifiable. In this study large volumes of release media and constant stirring of samples minimised the formation of a stagnant mass boundary transfer layer and ensured sink conditions were maintained.

The loaded hydrogel samples were placed in vials containing 10mls of chosen release medium (phosphate buffered saline, pH4 buffer or Octanol) which were then placed on a shaker. All release medium (10mls) was removed and replaced with fresh medium (10mls) at regular intervals. Absorbance values of the removed media were measured with a Cecil CE404 colorimeter, at wavelengths of 624mμ and 626mμ, as described in section 2.5.1 Cumulative release concentration profiles are shown in section 5.7

Use of octanol as a release medium initially proved problematic in that hydrogel samples exposed to the octanol became brittle and deformed. This is likely to have been due to diffusion of water from the samples into the octanol by osmosis. Resultant changes in hydrogel structure, which are unlikely to occur in dermal applications, would affect the experimental release characteristics of the material. Saturation of the octanol with water eliminated this problem but the water soluble model compounds partitioned into the water within the octanol and were distributed as globules within the release medium. This made accurate colorimetric assessment of release impossible. It should also be noted that potential exists for this water to include a portion of water from the hydrogel. Any methanol remaining within the hydrogel after equilibration will dissolve into the octanol reducing the water capacity of the hydrogel and forcing water out of the material. The semi-batch nature of this study would result in the disposal of small amounts of the water from the hydrogel with each measurement, eventually resulting in removal of all of the water from the hydrogel.

The apparent ideal would be to remove any excess water from the octanol whilst leaving sufficient to saturate the solvent. Use of small concentrations (0.02-1.0%) of desiccators magnesium sulphate and calcium chloride to remove excess water proved unfeasible as neither would fully dissolve within the octanol. Instead the octanol was passed through filter paper to remove the excess water prior to its experimental use.

5.7 The effect of drug properties on release: experimental results

It is the commonly held belief that hydrogels loaded with an active compound simply "dump" the solute from their aqueous component and that no potential exists for the control of this release to suit specific applications. In the topical delivery of drugs it is important that release rates are not a limiting factor for absorption of the drug. A release rate equal to or greater than the rate of elimination of the drug from the delivery site will ensure a constant supply of the drug for absorption into the skin. Conversely, in applications that require delivery of a compound at a rate below the rate of absorption through the skin, release must be the limiting factor for delivery and this control must be exerted by the chosen delivery vehicle. As a starting point in the investigation of the development of partially hydrated hydrogels as release systems, it is important to establish profiles of release of solutes from typical hydrogel compositions under various specific experimental conditions.

5.7.1 Effect of solute concentration

Release of a model compound from a typical hydrogel composition, used in contact lens production, into a typical release medium was measured. Bromopyrogallol red was loaded into HEMA contact lenses from 1% and saturated solutions according to method 5.6.3 and released into phosphate buffered saline (pH7.4), a typical release medium. Release profiles for both loading concentrations were plotted according to the procedure described in section 5.6.4.

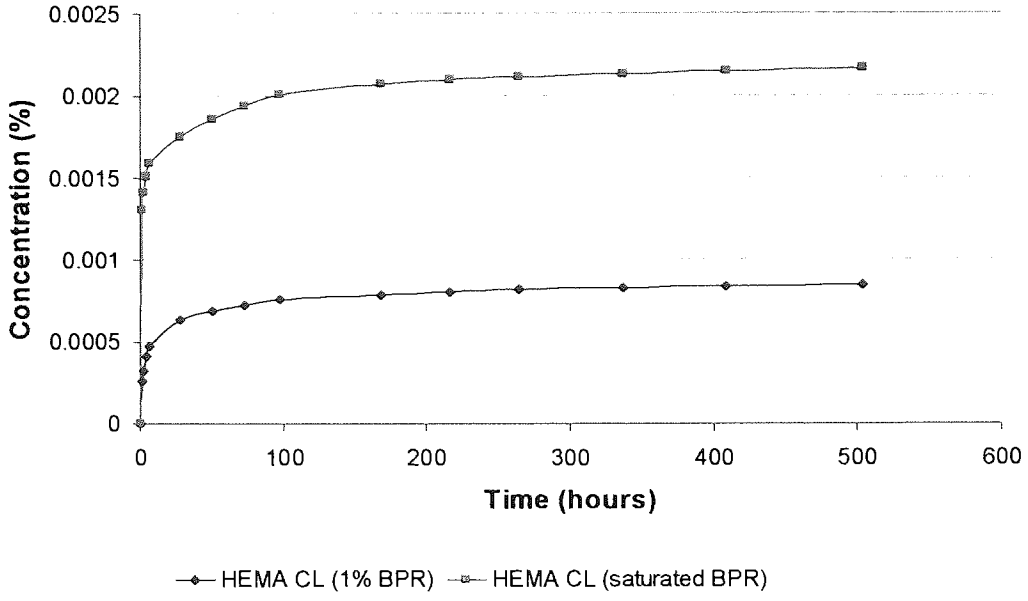


Figure 5.12 Release profiles for different initial loading concentrations
Cumulative release of bromopyrogallol red from HEMA contact lens material into aqueous release medium (PBS) at two loading concentrations, 1% and saturated solution as inferred from Figure 5.5; calibration curve for BPR in PBS at 626mμ.

Variation of initial loading concentration did not alter the profile of release from the hydrogel but rather amplified and extended the delivery period. Specifically, an increased loading concentration resulted in release of greater quantities of the model compound and an extended period of approximately first order release before the retention phase. The use of higher initial loading concentrations of a compound in hydrogel release devices will be useful in allowing increased dosage levels to be administered over prolonged delivery periods.

The release profile follows the typical 3 stage release process that was predicted in section 5.2.4. An initial rapid "burst" release of the compound occurs within the first few hours of release. The burst phase is followed by a second phase of approximate first order release of the compound. The third phase can be described as a "no-release" phase. Here, there is retention of some loaded compound within the polymer matrix which only releases at an infinitesimally slow rate into the phosphate buffered saline.

Although an initial "dump" of the model compound from the aqueous component of the hydrogel was observed, the presence of a second stage of release during which release appears to be approximately first order is promising for the use of hydrogels in controlled release. Manipulation of these stages of release could be used to develop a material which will provide an initial reservoir of a drug at the delivery site that can be maintained by the subsequent first order release of the compound; ensuring a constant supply of the compound as it is absorbed by the skin. Development of such a material requires that the determining factors that shape this release profile are first identified. These can then be used as a basis for modification of the material's release characteristics accordingly. The logical first stage in the process is the analysis of the interaction between hydrogels and loaded compounds, and the effects these have on release. The relative influence of the properties of each provides the key to the development of hydrogel compositions from which release of a compound can be pre-determined. A systematic study of the influence of the structural properties of hydrogels and release compounds on their interaction with each other and the subsequent release of the compound follows.

5.7.2 Effects of polarity of solute

The polarity of a compound indicates its affinity for other polar molecules including water; the more polar a compound, the greater its hydrophilicity. The polar ionised form of a compound can therefore be expected to have a lower affinity for the hydrophobic polymer backbone of a hydrogel than its unionised counterpart. Theoretically therefore, the release profile of the ionised form of a compound will differ from that of the compound in its unionised form, dependent on the hydrophilic nature of the of the hydrogel from which it is being released.

The indicator dye Fluorescein and its sodium salt (NaFl) were chosen as models to study the effects of polarity of a solute on its release. The increased molecular size of NaFl conferred by the presence of the sodium ion is minimal, allowing an objective study of the effects of ionisation and polarity on release from a particular hydrogel composition. Contact lenses (HEMA) were loaded with 0.1% solutions of the ionised and unionised forms of a model compound, fluorescein, according to the method described in section

5.6.3. Profiles for release into PBS (pH 7.4) were measured over a reduced time period of 80 hours in recognition of the shorter release period observed at reduced initial loading concentrations. Figure 5.13 shows the release profiles for both forms of the compound.

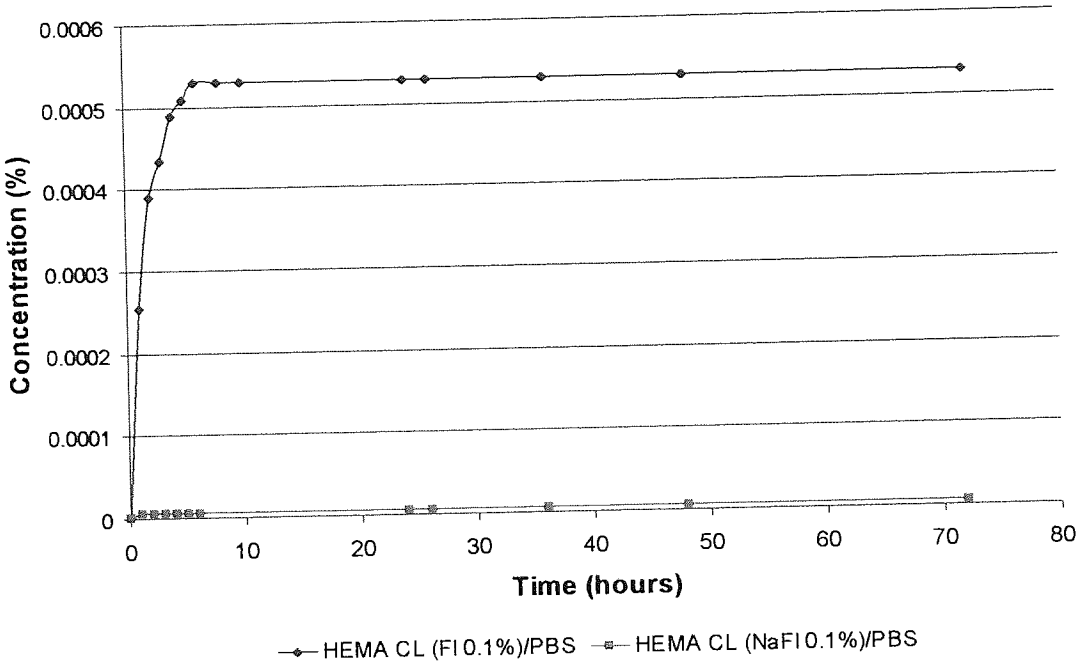


Figure 5.13 Release profiles for ionised and unionised forms of a compound.
Release of ionised and unionised forms of fluorescein from HEMA contact lenses into aqueous release medium, PBS, as inferred from Figure 5.8; calibration curve for NaFl in PBS at 624mμ.

Though this experiment was intended as a study of the effects on release of interactions between different forms of a compound and the polymer backbone of the hydrogel, the influence of the external release environment must be taken into account in analysis of the results. The pKa of fluorescein (pH 6.4) dictates that the compound will be converted to its ionised form in an environment of higher pH, as in the PBS release medium (pH = ~7). It is therefore reasonable to conclude that any fluorescein released into this medium will be ionised to Fl^-. For this reason, concentrations of release samples were calculated using the calibration curve for NaFl in PBS (figure 5.8)

The greater solubility of Fl^- in aqueous media compared to that of fluorescein in its unionised form (Fl) indicates that the release of NaFl (i.e. Fl^-) will be greater than the release of Fl under these experimental conditions. The burst phase of release of any

unbound dye will be much slower for the sample loaded with Fl on account of the time taken for conversion of the dye to its more soluble form. Though the release profiles shown in figure 5.13 show this not to be the case it would seem unlikely that release of Fl^- (NaFl) into PBS would be as limited as is indicated by the release profile. It is proposed that rehydration of the loaded hydrogel samples in PBS during their preparation was most effective in aqueous extraction of Fl^- from the NaFl-loaded samples and as a result the profile shown does not illustrate the burst phase of release. This is further supported by the apparent lack of a secondary phase of approximate first order release of Fl^- (NaFl). The high solubility of this form of the compound and the associated lack of affinity of the molecule for the relatively hydrophobic polymer backbone suggests that, as proposed by sceptics to the use of hydrogels in controlled release applications, Fl^- will simply be "dumped" from the hydrogel under these conditions. The greater hydrophobicity of Fl increases the affinity of the compound for the polymer backbone, hindering the release of Fl and resulting in the second, approximately first order, phase of release seen between hours 2 and 6.5 of the release experiment.

The effects of solute concentration and ionisation have both been shown to influence release but the study of the effects of ionisation (polarity) of a compound on release has confirmed that hydrogel composition and external release environment also play a vital role in determining the release characteristics of a specific hydrogel release system. Hydrogel composition and resultant affinities of compounds for the polymer backbone of a hydrogel can greatly hinder release; a phenomenon that might be exploited in the development of hydrogels for controlled release applications. The effects of hydrogel composition on release and their role in solute:polymer interaction were studied in more detail in section 5.8.

5.8 Effects of hydrogel composition on release

Two key variables were identified as being important in the study of the effects of hydrogel composition on release of loaded compounds. These were the hydrophilicity/hydrophobicity of the polymer backbone of the hydrogel and the EWC of the hydrogel (samples studied here were fully-hydrated. In the case of partially hydrated samples, degree of hydration should also be considered).

Examination of release from HEMA hydrogels has given information about the influence of a hydrogel with a specific equilibrium water content and structure on release. By comparing release of a compound from HEMA to its release from other neutral, fully-hydrated hydrogel compositions, the effects of differences in hydrophobicity of polymer backbone, the presence of hydrophilic groups on the polymer sidechains, and the EWC of the gel (and its conferred affinity for hydrophilic compounds) can be observed.

Another longstanding contact lens material is *N*-vinyl pyrrolidone (NVP), a hydrophilic monomer with a structure quite different to that of HEMA (structures are detailed in section 2.2). The hydrophilicity of NVP prevents its polymerisation as a homopolymer hydrogel; it must be co-polymerised with a less hydrophilic monomer, such as MMA, if it is to maintain its structural integrity when swollen with water. This copolymer is known commercially as Lidofilcon and was approved by the FDA in the early 1970s for use in the eye. In the context of these experiments, the presence of MMA will not cause complications to results analysis as this neutral monomer will not bond water. The greater hydrophilicity of NVP compared to that of HEMA is accompanied by a significantly higher EWC of the hydrogel; 67% compared with 38%.

Copolymerisation of two monomers within a hydrogel in this way is often used as a means of combining contrasting or complementary characteristics of the two monomers within one material. The amide group present in monomers such as NVP and AMO is more hydrophilic than the hydroxyl group of HEMA and co-polymerisation of HEMA with these monomers can be used to produce hydrogels with greater EWCs. Meanwhile, the CH_2 groups of their cyclic structures convey a higher lipid solubility of these monomers than HEMA. The mixture of more hydrophilic and more hydrophobic

segments of these monomers than HEMA, in the context of release, will confer different affinities of the hydrogel polymer backbone and its sidechains for loaded compounds, and with these, different profiles of release. Details of the four hydrogel compositions described are given in table 5.2. These compositions were used to study the effects of hydrogel composition on release of a neutral compound.

Bromopyrogallol red was loaded into the four different hydrogel compositions; HEMA contact lenses, MMA-NVP contact lenses, HEMA:AMO membrane, and HEMA:NVP membrane, from saturated solutions and released into phosphate buffered saline (pH7.4), a typical release medium. The different compositions were anticipated to have different affinities for the compound, based on their water/octanol partition co-efficients (relative hydrophilicities)*; the more hydrophobic hydrogel compositions (less negative Ko/w) were anticipated to have much greater affinities for the hydrophobic BPR (Ko/w = +4.32). Release profiles for the four compositions are shown below.

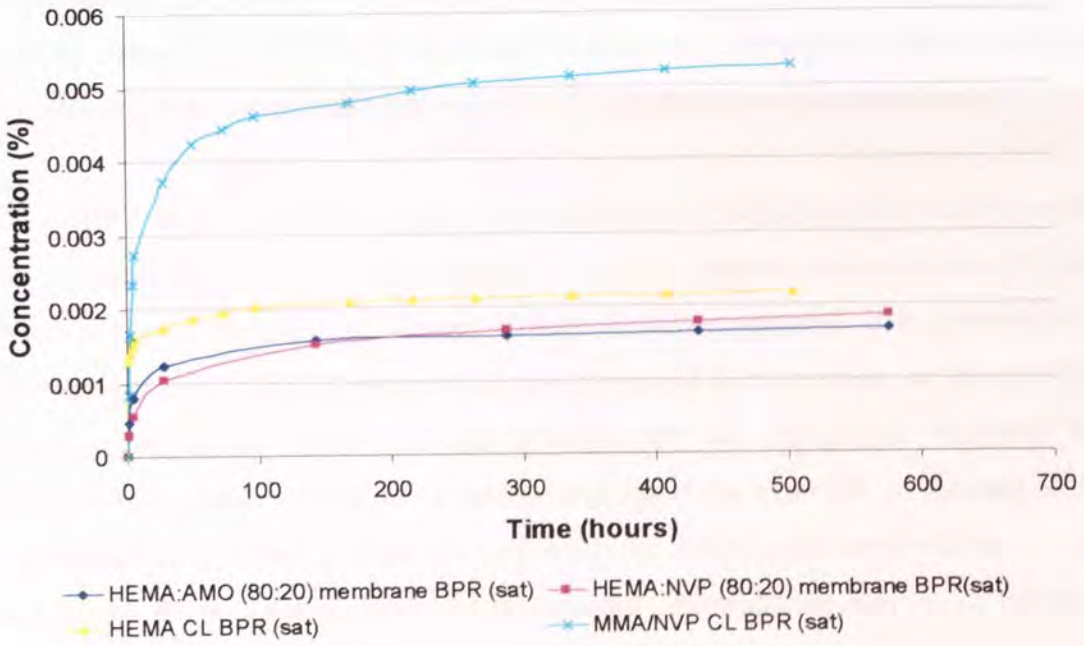


Figure 5.14 Release profiles for different hydrogel compositions
Cumulative release of bromopyrogallol red from various hydrogel compositions into aqueous release medium, phosphate buffered saline, as inferred from Figure 5.5; calibration curve for BPR in PBS at 626mμ.

* Log $K_{o/w}$ values for monomers:
NVP = 0.38 HEMA = 0.30
MMA = 1.28 AMO = - 0.37

Comparison of release profiles of bromopyrogallol red into phosphate buffered saline from the different hydrogel compositions studied gives information about the affinity of the model compound for the polymer materials.

Release profiles for both copolymer membranes were very similar, as would be expected with regard to their equal EWCs. These compositions demonstrated a lower tendency to release bromopyrogallol red than either of the contact lens materials. However, quantitiatively, release of BPR from all of the materials was significantly greater (at least 2-fold) than the release observed for Fl in previous experiments. The secondary phase of approximate first order release from HEMA:AMO membrane, HEMA:NVP membrane, and indeed, HEMA contact lenses were all considerably shorter than that seen for the MMA:NVP contact lens material.

The strongly lipophilic tendency of bromopyrogallol red ($K_{o/w}$ +4.32) attracts this molecule to the lipophilic cyclic structures of AMO and NVP. Release of bromopyrogallol red from the hydrogel membranes containing these monomers is hindered by interactions between the dye and the hydrogel. Indeed, the membranes were seen to release much lower concentrations of BPR than the contact lens materials.

Release of BPR from the HEMA contact lens material was slightly greater than from the hydrogel membranes and can be explained by the greater hydrophilicity of this composition giving the material a lower affinity for the compound. It is interesting to note the slightly shorter second phase of release compared with that seen for the hydrogel membranes. The lower affinity of the hydrogel for the compound increases the availability of free solute for diffusion through and out of the hydrogel. In the case of the hydrogel membranes, where a greater proportion of the loaded compound will be associated with the polymer backbone of the materials, the resultant delay in diffusion of the compound has produced a longer second phase of release.

Release of bromopyrogallol red from the MMA:NVP contact lens composition was far greater than from the other compositions through both a much greater "burst" release phase over an extended period and an extended second release period of approximate first order release. This can again be attributed to the greater hydrophilicity of the polymer backbone of the material and associated reduction in affinity of the loaded

compound for the polymer. The greater EWC of the NVP:MMA hydrogel compared to that of the other compositions studied aids diffusion of the BPR towards the hydrogel release surface.

The influence of the polymeric component of the hydrogel, as demonstrated in these results, can be used in the manipulation of release of a compound from a hydrogel. Modification of the hydrogel composition to include polymeric components of greater or lesser hydrophilicity can be used to regulate interactions between a loaded compound and the polymer backbone of the hydrogel. In this way, release profiles of the compound can be adapted for an intended application. Both the burst phase and the second release phase can be modified with respect to their intensity and duration, according to the release requirements.

5.9 Examination of the kinetics of hydrogel release systems

By inspection it appears that the concentration/time release profile for release from neutral fully-hydrated hydrogels resembles, in part, a first order kinetic curve. This would imply that the ratio of release is, during that period, proportional to the concentration of remaining material. Although release from hydrogels is likely to be a complex rather than simple process it is logical to explore the use of a conventional first order kinetic plot in interpreting the results.

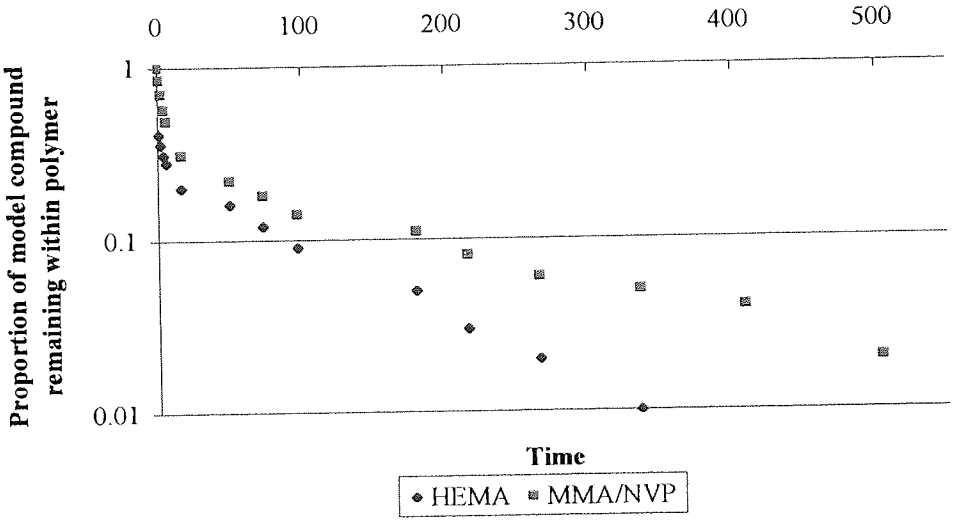


Figure 5.15 First order kinetics profile of release
First order plot of release of bromopyrogallol red into phosphate buffered saline

Figure 5.15 shows the data presented in the form of such a plot. The plot suggests that there is indeed an initial rapid burst phase of release followed by a period of substantially first order release. The length of this period of approximate first –order release is clearly shown in this plot to extend over 300 hours of release, a promising sign in the assessment of the suitability of this group of materials for controlled release applications. There is additionally a proportion of the model compound that remains unreleased at the end of the experiment. Extending the time period did not produce any significant further release of this "firmly-bound" material. In the development of hydrogel release systems the amount of any particular compound remaining after release must be considered both in terms of "drug" wastage and safe disposal of spent devices.

5.10 Partitioning stages involved in release from hydrogels

Drug release from a hydrogel can be considered to consist of a series of partitioning stages shown in figure 5.16. The pKa of a drug and the pH of its environment govern the degree of ionisation of the compound as described in section 5.2. In the first stage of release a loaded drug is partitioned between the aqueous and polymeric components of the hydrogel. The degree of this partitioning is determined by water-octanol partition coefficients of the ionised and non-ionised forms of the drug, which control the affinity of each species for each of the two phases. The hydrophobic polymeric portion of the hydrogel will be the favoured environment for hydrophobic non-ionised species. Hydrophilic ionised forms of a compound will partition favourably into the water within the polymer network. The ionisation of the drug will be determined by the pH of its environment. Should the pH within the environment change, or should the drug be transported to an environment with a different pH, its degree of ionisation will be affected according to its pKa (section 5.2.3).

The water-octanol partition coefficients of the ionised and non-ionised forms of the drug also govern their subsequent release from the hydrogel into the lipoidal and aqueous components of the biological interface, or in the case of experimental studies the external release medium. More hydrophobic compounds (less negative Ko/w) will partition more readily into a lipophilic environment than into a hydrophilic environment, and vice versa for more hydrophilic compounds. In summary, transport of a drug from a hydrogel to the site of delivery is affected by the cumulative effect of each of these individual stages and each offers the potential for manipulation of the release profile of a compound.

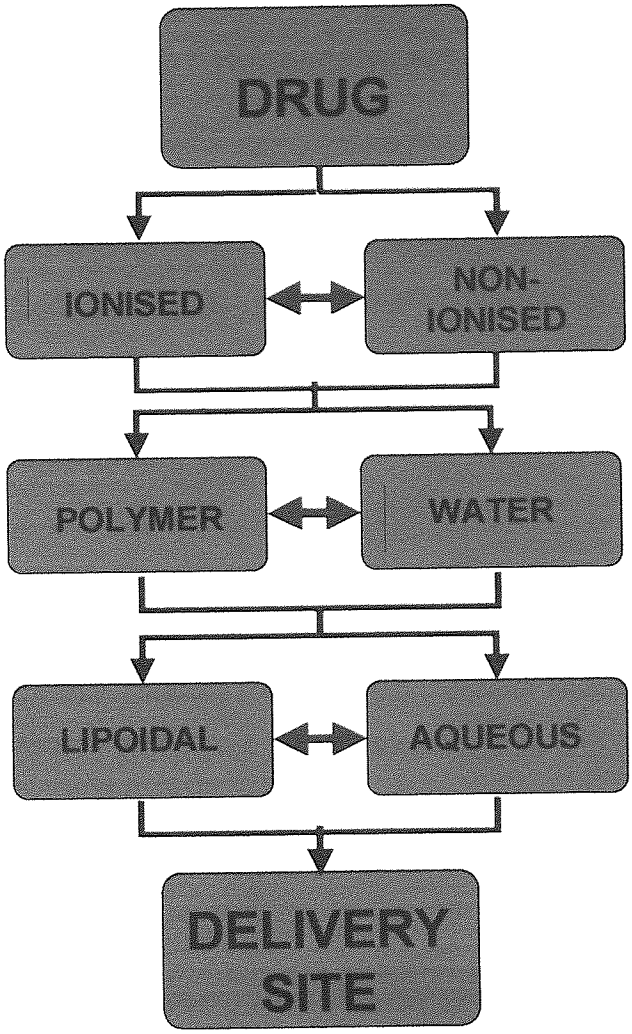


Figure 5.16 Flow chart showing the partitioning stages involved in release of a compound from a hydrogel

5.11 The effects of external environment on release

Previous experiments examined the profile of release of a solute from neutral, fully hydrated hydrogels and studied the effects of drug properties and hydrogel composition on release independently of the influence of the release environment. Figure 5.16 shows however that the nature of the external environment plays an important role in distribution and release. The influence of the external release environmental conditions i.e. release medium will now be examined.

Release behaviour of an ionisable drug from fully hydrated neutral hydrogels into the different release media will be modelled using an ionisable pigmented compound; fluorescein. An organic release medium (octanol) and a second aqueous release medium at a pH well below the pKa of the fluorescein model compound will be used to examine how the hydrophilicity and pH of the release medium each affect the release of an ionisable compound.

5.11.1 Effects of pH of external release environment on release from HEMA contact lenses.

The effects of pH of the external release environment on release of a compound from neutral fully hydrated hydrogels were studied. Hydrogel samples (HEMA contact lenses) were loaded from 0.1% solutions of fluorescein in its unionised form, which remains stable at a pH below its pKa (pH 6.4). Release experiments were carried out in aqueous media at pH above the pKa of fluorescein (PBS; pH ~7) and below the pKa of fluorescein (aqueous buffer; pH 4). The pH of the release medium at the hydrogel surface will influence the ionisation state of the compound here. The effects of any resultant changes to the ionisation of the compound on its release from the hydrogel were compared.

Release into aqueous pH4 buffer, well below the pKa of fluorescein (pH6.4) will not affect the ionisation of the compound. The presence of phosphate buffered saline at the release surface however, will increase the pH at the release site, resulting in ionisation of the fluorescein to its more water-soluble form (Fl^-). For this reason, concentrations of

these release samples were calculated using the calibration curve for NaFl in PBS (figure 5.8). Comparison of release of fluorescein into the two media will allow unambiguous study of the effects of pH of external release media on the ionisation state of a drug and its associated solubility in an aqueous medium. In terms of water/octanol partition co-efficient, both media present comparable systems and as such the unequivocal effects of external media pH will be represented by the results.

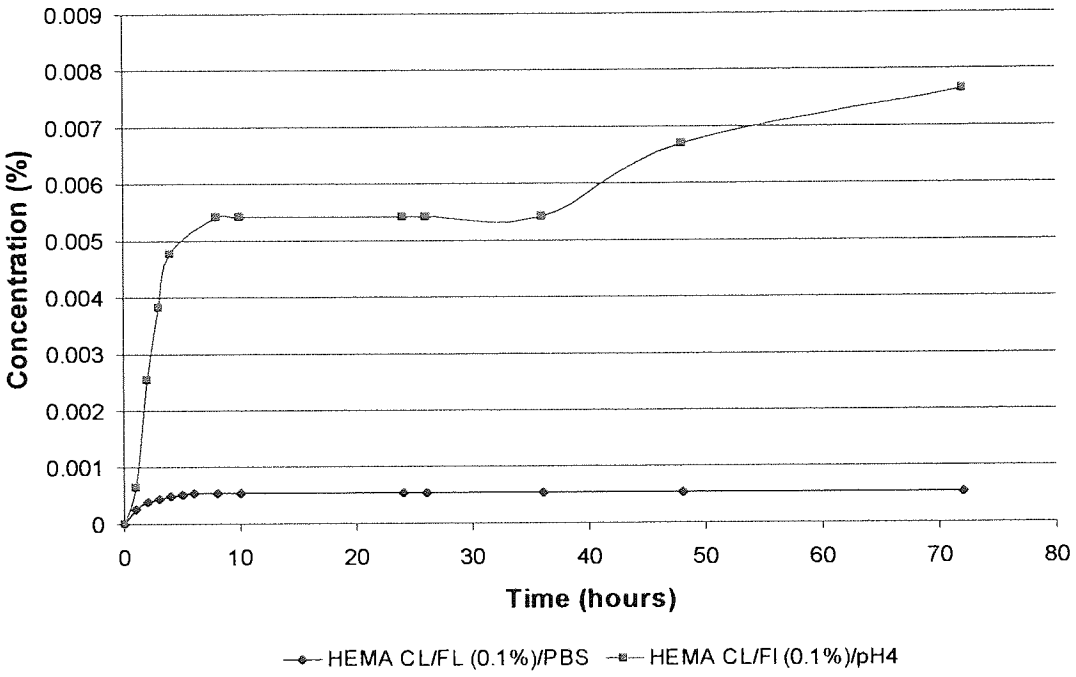


Figure 5.17 Release profiles into media of different pH

Cumulative release of fluorescein from HEMA contact lenses into aqueous media at different pH (PBS and pH4 buffer), as inferred from Figure 5.8; calibration curve for NaFl in PBS at 624mμ, and Figure 5.7; calibration curve for Fl in pH4 buffer at 624mμ respectively.

Much of the fluorescein at the surface of the hydrogel in the PBS release system will have been converted to its ionised form. In recognition of this, concentrations of release samples from this system were calculated from the calibration curve for NaFl in PBS (figure 5.8). Effectively therefore, the release of two different compounds with very different aqueous solubilities is now being studied in the two release systems. The acid form of a compound, in this case fluorescein in its unionised form, is always less soluble in aqueous media than the ionised form of the compound.

It was anticipated that the difference in degree of ionisation of the compound at the release surface of the two systems and the differing aqueous solubility of the two forms of the compound would be reflected in the release profiles seen for the systems. It would seem reasonable to expect that the fluorescein at the release surface of the PBS system, in its more soluble ionised form at this pH, would be released quite readily into the aqueous release environment. The less hydrophilic, unionised form of the compound prevalent at pH4 was expected to reduce the release of the compound into the external medium, most noticeably during the burst phase of release.

The release profiles shown in figure 5.17 indicate this not to be the case, instead showing a significantly smaller burst phase of release into PBS than into pH4 aqueous buffer. As suggested in section 5.7.2, the effective aqueous extraction of very soluble compounds during the equilibration stage of sample preparation may have influenced the results obtained so that effectively, the profile for HEMA CL/Fl (0.1%)/PBS represented in figure 5.17 is post-burst release.

In the case of the HEMA CL/Fl (0.1%)/pH4 system, re-equilibration in pH4 will have resulted in the extraction of much less of the loaded compound in its less soluble acid form. The profile seen in figure 5.17 shows an extended period of secondary release from the sample. This slow release of the compound can be attributed to the delay during which fluorescein is partitioned between the hydrogel polymer backbone and the aqueous component of the hydrogel from which it can subsequently be released.

The secondary effect of interactions between the compound and the polymer component of the hydrogel, as represented in figure 5.16, must be considered in analysis of the release profiles of the compound. The two forms of the compound will interact with the polymer backbone to a different extent which will affect the second stage of the release process. The structure of the acid form of the drug facilitates increased polymer-compound interactions. These will reduce the amount of "free" solute available for release and will additionally delay diffusion of the compound to the release surface during the second phase of release, limiting secondary phase release rates of fluorescein in its acid form. The hydrophilic nature of the ionised form of the compound has a much lower affinity for the polymer backbone and favours its partition into the aqueous medium from the relatively hydrophobic environment within the hydrogel. This is likely

to result in much of the loaded compound being released during the burst phase of release and give a shorter, less intense, secondary phase of release. A reduced fraction of the initial loading concentration is likely to remain in the hydrogel under these release conditions.

If, as suggested, we assume that the release profiles plotted in figure 5.17 are post-burst release, the first sections of the profiles show the second phase of the release process. This phase is much greater for release of fluorescein into pH4 aqueous buffer and continues over an extended time period. As in section 5.7.2, it is proposed that the limited secondary phase of release observed for fluorescein (Fl^-) into PBS is further indication that a large proportion of the "free" compound was readily removed during the equilibration stage of sample preparation. The release of some dye during this phase (notably not seen in the profile for release of NaFl (Fl^-) into PBS) is attributed to interactions between the compound and the polymer backbone. Post burst release, the remaining fraction of the loaded compound is partitioned between the polymeric and the aqueous portions of the hydrogel see figure 5.16. That which is partitioned into the aqueous portion of the hydrogel is then free for diffusion and release in the second phase of the release profile.

A lesser proportion of the initial loading concentration was removed from the HEMA CL/Fl (0.1%)/pH4 sample after equilibration, and as a result, a greater amount was available for subsequent partition into the aqueous portion of the hydrogel and release during the second phase of the release profile. The delayed release of the compound in this way can potentially be exploited in controlled release applications.

In both samples, the hydrophobic tendencies of fluorescein in its acid form, in which it was loaded, give the compound an affinity for the polymer backbone of the hydrogel, slowing release and retaining a proportion of the compound in the hydrogel post-release.

The influence of the external release environment on release characteristics of a compound is important with respect to the variations in pH seen at different delivery sites. The pH of tears is around pH7 making release into phosphate buffered saline a parallel to release into the ocular environment. Release into pH 4 buffer more closely represents release onto skin (pH5). Use of media of different pH in this way provides a

good indication of the likely influence of the pH of different body sites on release and indicates the importance of consideration of the influence of external pH on drugs with different pKa values.

5.11.2 Release into an organic release medium from HEMA contact lenses.

The release profiles for fluorescein into aqueous media pose the question of whether there is a more effective method of extracting the non-ionised, less water-soluble, form of the compound from the hydrogel that could be exploited in clinical applications to achieve greater dosage levels and reduced drug wastage.

If we refer back to the partitioning stages of release shown in figure 5.16 we can see that lipoidal/aqueous nature of the release environment is the final determinant of partitioning of a compound between a hydrogel and the delivery site. The non-ionised acid form of a drug will be more soluble in a lipophilic, organic medium than in an aqueous medium. Partitioning of such a compound between the partially aqueous hydrogel and an organic medium, rather than an aqueous medium, will favour release of the compound from the hydrogel.

However, the polymeric component of the hydrogel also has a greater affinity for the non-ionised, hydrophobic form of the compound than for the hydrophilic ionised form. Consequently, the polymer backbone of the hydrogel and the organic release medium will be in competition for the compound. Release of the drug from the hydrogel will depend on this competition which itself depends on the prevalence of hydrophobic components of the hydrogel and the pKa of the compound.

Though generation of an accurate calibration curve for fluorescein in octanol had not proved possible this experiment was run as a secondary verification of the technique, in the hope that release of fluorescein into aqueous and organic media could be compared. Hydrogels (HEMA) were loaded from 0.1% solutions of fluorescein and released into octanol, according to method 5.6.4.

As observed in attempts to generate a calibration curve for fluorescein in octanol, most release samples were colourless or had absorbencies that were too low to register on the colorimeter used here. On initial analysis interactions between the fluorescein acid and the polymer backbone appear to have hindered release of the compound to such an extent that reasonable concentrations were infrequently observed. Though this may go some way towards explaining what has happened within the release system, the inconsistency of results dictates that the probability of experimental error should also be considered. Problems experienced in preliminary release work during the development of these methods (detailed in section 5.6.4) may have resulted on poor colorimetric representation of concentrations of fluorescein within release samples. This reinstates the possibility of increased release and dosage of hydrophobic compounds to lipophilic sites. In order to verify this hypothesis, an alternative method of measuring release, such as High Performance Liquid Chromatography (HPLC) must be employed.

Though the competition between the hydrogel and octanol could not be examined, any differences in the release profiles of fluorescein into aqueous and organic media will provide an important indication of how the compound might be released onto human skin. Sebaceous and intracellular lipids within the skin create a hydrophobic environment that has a hydrophilic component in the form of aqueous ducts. Sweat from these ducts maintains a pH of around 5 at the skin surface. Release of fluorescein and similar compounds from hydrogels onto the skin could be anticipated to follow a combination of the profiles seen for release of the compound into octanol and pH 4 aqueous medium.

Previous experiments have demonstrated the important influence of polymer/drug interactions on drug release from hydrogels. By altering the competition between the polymer backbone and the release medium release profiles could be modified. Alterations to the polymer backbone provide a means of shifting this competition. If release profiles can be altered in this way, modification of the polymer component of hydrogels will allow the control of release.

5.11.3 Release into aqueous and organic release media from MMA-NVP contact lenses.

Previous experimental work has examined the individual partitioning stages of release from a hydrogel, depicted in figure 5.16, and has demonstrated the influence of hydrogel composition on release of a neutral compound (section 5.8). The role of interactions between a loaded compound and the polymer backbone of a hydrogel release vehicle, in particular with reference to differences in these affinities with different ionisation states of a compound, has also been observed. The interdependent role of the different stages of partitioning of an ionisable compound will now be examined. Release of fluorescein from HEMA contact lenses into the two aqueous media studied here will be compared with release of the compound from MMA:NVP contact lens material (composition details in table 5.2) under the same experimental conditions.

Release of fluorescein from fully hydrated MMA-NVP hydrogels into PBS was compared to its release from the HEMA material. As in previous experiments, the hydrogels were loaded from 0.1% solutions of the compound as described in 4.6.3. Release profiles for both compositions are shown in figure 5.18.

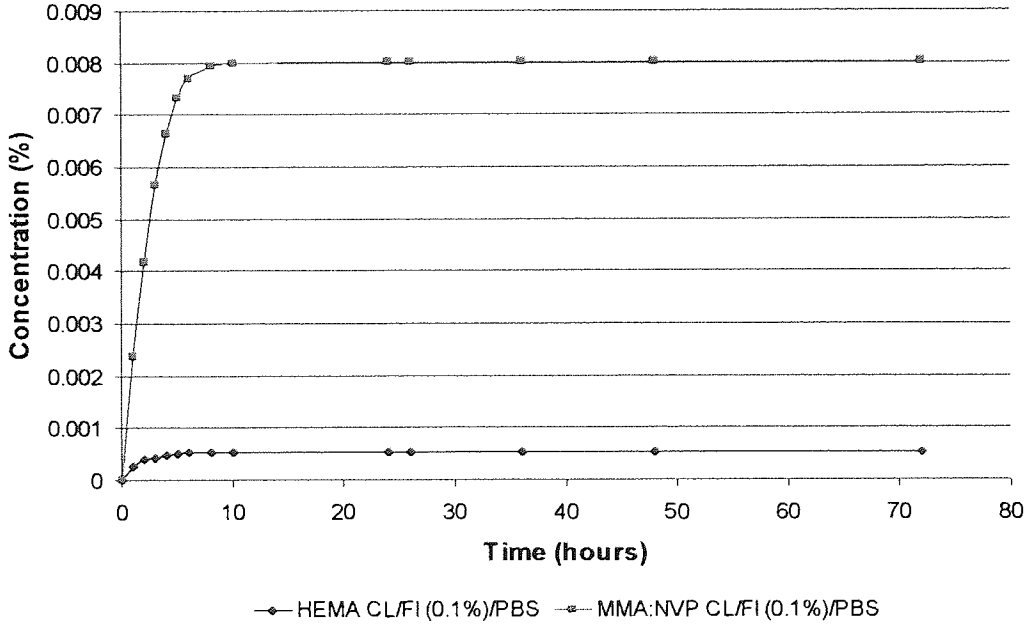


Figure 5.18 Cumulative release of fluorescein from different hydrogel compositions into aqueous media, phosphate buffered saline.
As inferred from Figure 5.8; calibration curve for NaFl in PBS at 624mμ.

Release of fluorescein into PBS from MMA:NVP contact lenses was considerably greater than from HEMA contact lenses. The fluorescein present at the release surface in a PBS release system will be converted to its hydrophilic ionised form, Fl^-. For this reason, concentrations were calculated using the calibration curve for NaFl (i.e. Fl^-) into PBS (figure 5.8). In this form the affinity of the compound for the polymer backbone of the MMA:NVP hydrogel can be anticipated to be greater than its affinity for HEMA due to the amide group of the NVP. As a result, the burst phase of release from HEMA would be expected to be greater than that from MMA:NVP.

Once again it would seem sensible, considering the previously discussed evidence to support the theory, to assume that some of the unbound fluorescein at the release surface of the hydrogels was ionised and aqueously extracted during equilibration of samples in their preparation. The lower affinity of fluorescein for HEMA leaves a greater proportion of the loaded compound free for aqueous extraction at this stage. This has effectively eliminated the burst phase of release from these experimental studies. The large burst phase of release seen for MMA:NVP nonetheless might be attributed to the greater affinity and resultant higher initial loading capacity of the composition, and the slower, more complex process of diffusion of the compound out of the hydrogel.

The fluorescein remaining in the hydrogel samples after equilibration will interact more strongly with the CH_2 groups of the cyclic structure of NVP than with the polymer backbone of the HEMA homopolymer. This is demonstrated by the extremely short second phase of release from the MMA:NVP sample. By comparison, the second phase of release from HEMA begins at an earlier time point and continues over an extended period. Retention of a greater concentration of the compound is likely in the MMA:NVP hydrogel, again due to interactions between the polymer and the dye.

Release of fluorescein from the same hydrogel compositions into pH4 aqueous buffer was also compared to study further the differences in affinity of the ionised form of compound for the hydrogels.

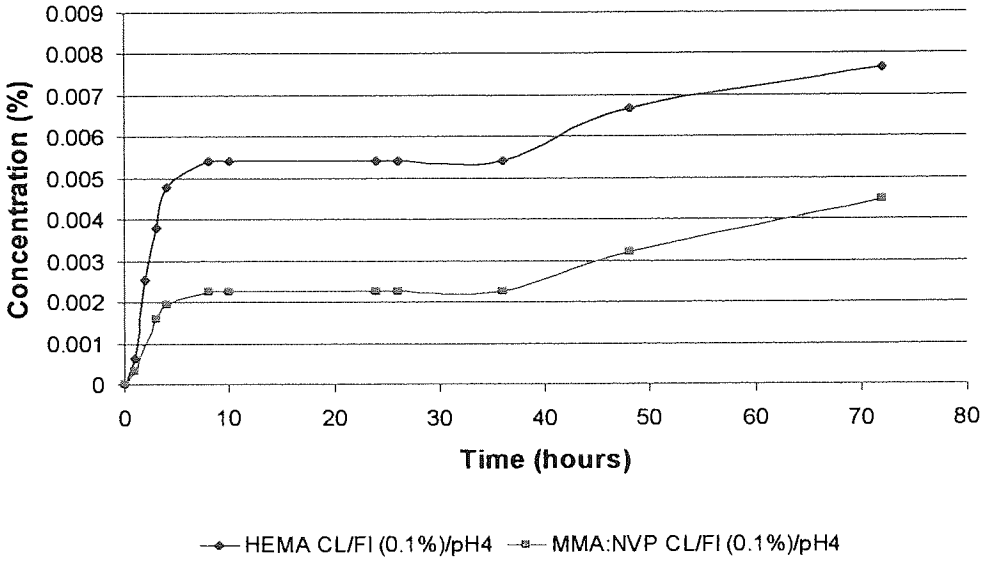


Figure 5.19 Release of fluorescein from two hydrogel compositions into aqueous pH4 buffered medium.
As inferred from Figure 5.7; calibration curve for Fl in pH4 buffer at 624mμ

Release of fluorescein from MMA:NVP contact lenses into pH4 buffer was much lower than release from HEMA contact lenses as expected. Despite the higher EWC that results from the hydrophilicity of the NVP within the hydrogel, the lipophilic acid form of fluorescein has a high affinity for the CH_2 groups of the cyclic structure of NVP and its partition into the external aqueous must compete with this. These interactions between fluorescein and the hydrophobic groups on the polymer backbone result in high levels of retention of the compound even over long periods of release. The more hydrophilic nature of HEMA is less conducive to polymer retention of the compound and as such greater concentrations of the compound are released from this composition.

5.11.4 Release of the ionised form a model compound from HEMA and MMA:NVP

By incorporating fluorescein into the hydrogels in its ionised form the effects of ionisation of the compound by the external release medium on its release into PBS are eliminated. The direct effect of ionisation state of the compound on aqueous release can now be assessed. Release profiles for HEMA and MMA:NVP are plotted for comparison.

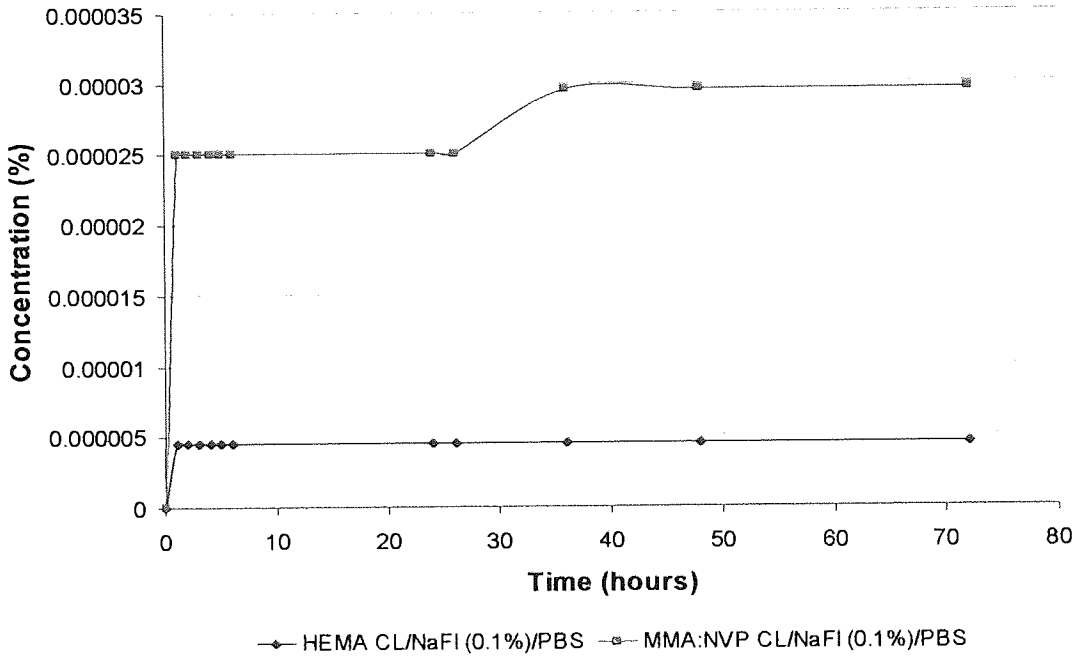


Figure 5.20 Release of fluorescein sodium salt from different hydrogel compositions into aqueous media

As inferred from Figure 5.8; calibration curve for NaFl in PBS at 624mμ.

Release of Fl^- (NaFl) into PBS was much greater from MMA:NVP than from HEMA in both the burst and secondary stages of release. The greater hydrophilicity of NVP (inferred by its amide group) and its higher EWC give the hydrogel a greater affinity for Fl^-, resulting in less aqueous extraction of the compound during the brief equilibrium period. The much larger burst phase of release seen for MMA:NVP can be attributed to a combination of several factors;

- The remainder of a greater proportion of the intial loading concentration of NaFl after equilibration, a result of the affinity of the ionised form of the compound for the hydrogel. The higher EWC of NVP:MMA compared to that of HEMA, and the hydrophilicity of its amide group reduce aqueous extraction during equilibration.
- Higher intial loading concentration, also a result of these characteristics.
- Removal of a greater proportion of the initial loading concentration from HEMA by aqueous extraction during equilibration.

The release profile for HEMA shows a distinct lack of a secondary phase of release. It would appear that any Fl^- not bound to the polymer backbone is favourably partitioned out of the low EWC hydrogel into the aqueous release environment during the burst phase of release, a reflection of the simple partitioning process taking place in this system, which is effectively a simple aqueous extraction in which equilibrium is reached very quickly.

The higher EWC and affinity of NVP for the dye creates a more complex partitioning process. After the intial burst phase of release, dye remaining within the hydrogel is further partitioned between the aqueous and polymeric components of the hydrogel. That which is partitioned into the aqueous phase can then diffuse out of the hydrogel in the second phase of release. This delay in release might be useful in the development of controlled release applications. However, the high affinity of Fl^- for the hydrogel ensures that a proportion of the compound will remain within the hydrogel.

Release of NaFl into pH4 aqueous buffer from the two hydrogel compositions was also compared. In an environmental pH below 6.4 (pKa of fluorescein) the ionisation state of the compound will be shifted, in the opposite direction to the ionisation changes previously seen, to its unionised, acid form. Concentrations of experimental samples were calculated using the calibration curve for fluorescein in pH4 aqueous buffer (figure 5.7).

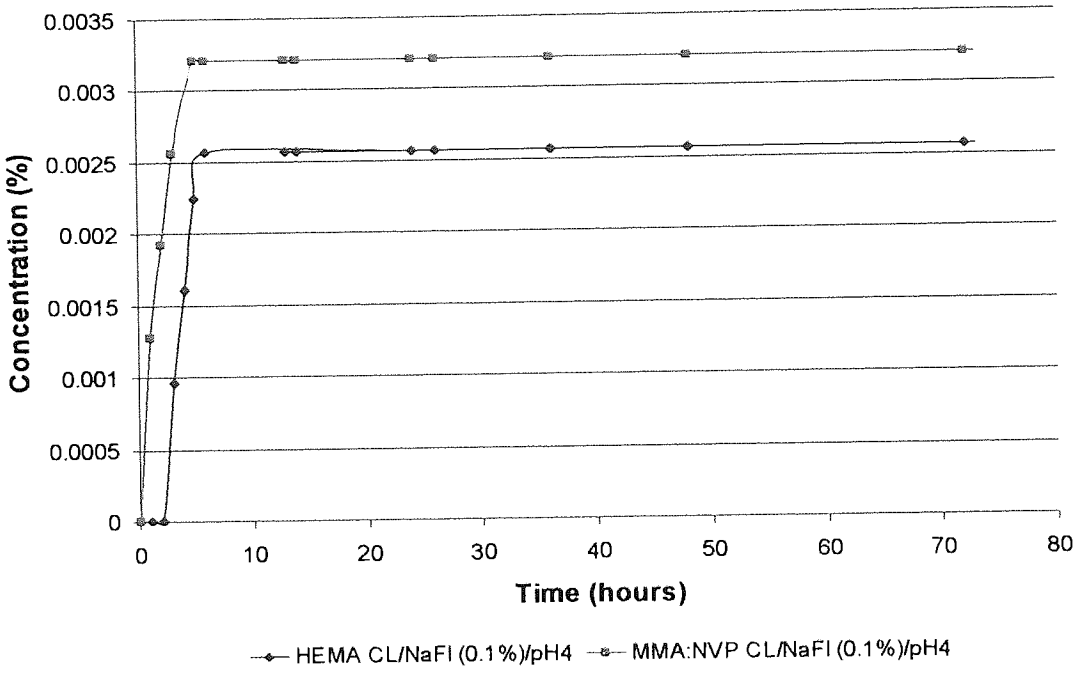


Figure 5.21 Release of fluorescein sodium salt from different hydrogel compositions into aqueous and organic media

As inferred from Figure 5.7; calibration curve for Fl in pH4 buffer at 624mμ

Conversion of the ionised form of fluorescein by pH4 buffer (ion suppression) was incomplete and as a result, release of the loaded compound into pH4 was around 50% of that observed for release of the non-ionised form of the compound from this polymer.

The release profiles shown in figure 5.21 indicate release of the compound from MMA:NVP to be greater than from HEMA, however both profiles follow a similar curve. The differences in release concentrations can be attributed to the favourable partitioning of the compound, loaded in its ionised form, out of the MMA:NVP hydrogel into the aqueous release environment, away from the lipophilic CH_2 groups of the cyclic structure of the monomer.

Comparison of figures 5.20 and 5.21 shows greater release was observed into pH4 aqueous release medium than into PBS. Extraction into pH4 is of fluorescein in a less fully ionised state than was the case with PBS extraction, thus there is more unionised fluorescein available for extraction by pH4 in the NaFl-loaded polymers than there is residual Fl^- that can be extracted by PBS post-equilibration. The first stages of the extraction process (aqueous equilibration) will have dramatically reduced the available NaFl (Fl^-) and has much less effect on Fl impregnated polymers.

Fluorescein in its ionised form was successfully diluted in octanol to give a calibration curve (figure 5.10) for calculation of experimental sample concentrations. Release of NaFl (Fl^-) from both hydrogel contact lens compositions into octanol was measured. The inability of octanol to change the pH at the release surface prevents any changes in the ionisation state of the dye. Figure 5.22 shows release profiles for both compositions.

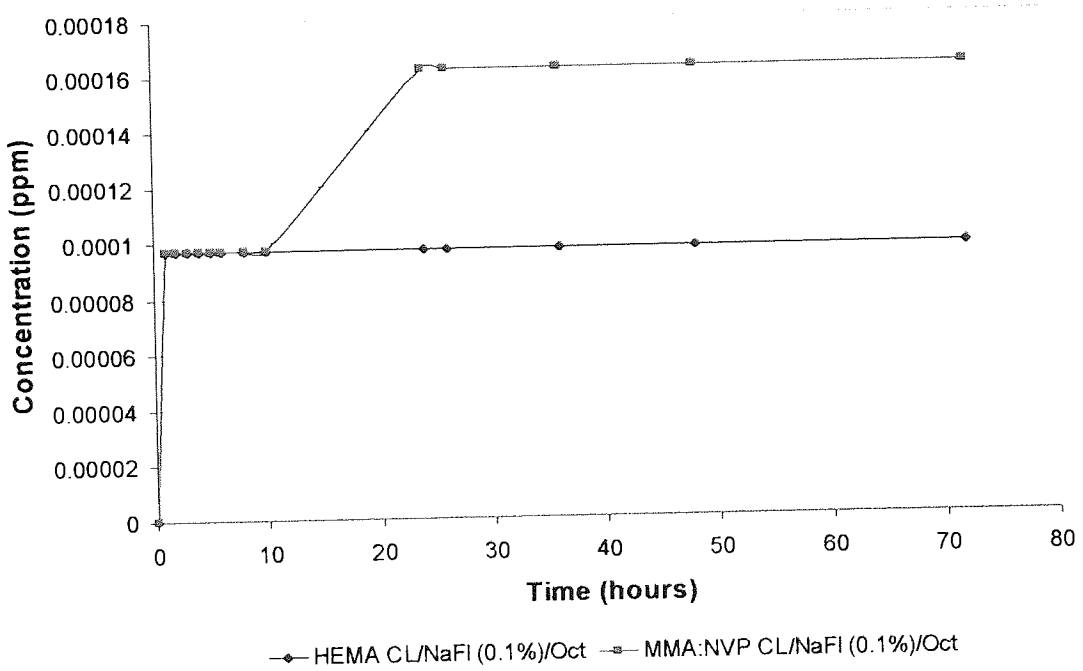


Figure 5.22 Release of fluorescein (sodium salt) from two hydrogel compositions into an organic release medium.

As inferred from Figure 5.10; calibration curve for NaFl in Octanol at 624mμ.

In an organic system, competition for partitioning of the compound is between octanol and water. Within the hydrogels, hydrophilic Fl^- will prefer the aqueous component of the hydrogel to its polymer backbone, however, the hydrophilic nitrogen-carbonyl group of NVP will give its copolymer a stronger affinity for the compound than has HEMA. Release of the hydrophilic compound into the lipophilic medium from the aqueous phase of both hydrogels can therefore be expected to be low. This is especially the case for MMA:NVP hydrogels where compound: polymer interactions will be greater, limiting the proportion of compound partitioned into the aqueous phase.

The profiles plotted show this not to be the case. No reasonable explanation for this could be found by the researcher and it is proposed that problems in accurate colorimetric measurement experienced for fluorescein in octanol have been mirrored here for the compound in its ionised form, giving inaccurate concentration values.

5.12 Discussion

Model compound studies of release were carried out as a means of identifying the role of various parameters in influencing and controlling release from hydrogels. This work has been successful in providing a qualitative insight into the characteristics of loaded compounds, hydrogels compositions, and external release environment that influence release, and into how these affect the interdependent stages of release to govern the release profile of a particular system. However, limitations to the methodology have been observed and should be noted accordingly for future reference.

- Initial loading concentration for samples loaded by imbibition cannot be accurately quantified. As initial loading concentration has been shown, within this program of research, to influence release, a more quantifiable loading technique or capability to quantify actual initial loading concentration is desirable.
- Equilibration of samples to their approximate EWC is associated with aqueous extraction of a loaded compound. This is particularly effective in the case of hydrophilic compounds such as NaFl and dramatically reduces the proportion of compound available for release. This gives much less intense release profiles for hydrophilic compounds than would be expected, effectively eliminating all or part of the burst phase of release.
- Dissolution of compounds in octanol can affect the absorbance of the compound to give misleading colorimetric measurements of the concentration of the solution. This was observed to be the case for fluorescein in octanol and possibly for sodium fluorescein in octanol also.

In the development of future experiments it is worth noting that strongly hydrophilic compounds do not want to stay in hydrogels and are rapidly released from the aqueous phase. NaFl is an example of a strongly hydrophilic compound (Fl^-) that is simply not retained within hydrogels. Studies with this compound have demonstrated experimentally the wide-held belief that hydrogels simply dump hydrophilic compounds from their aqueous phase. Though there is some modulation of the dye between its ionised and unionised states, its ready ionisation brings into question its worth in future studies for the development of hydrogels for controlled release. In order to exploit the potential of

hydrogels as controlled release systems, more complex partitioning systems must be employed. This can be achieved through choice of compound, hydrogel composition, and release environment.

Release from all of the systems studies followed the anticipated three-stage process discussed in section 5.2.4. The process of release began with an initial rapid burst phase during which the greatest concentration of release was seen. This was followed by a phase of linear approximate first order release. Finally, a portion of the drug is released at an infinitesimally slow rate such that it is effectively retained within the delivery vehicle.

This common kinetic release profile is conveniently represented by two expressions (Crank, 1956) valid for the different parts of the desorption curve. The early time approximation holds over the initial portion of the curve, that is, the release of the first 60% of the total drug is given by equation 5.4

$$Mt / Mo = \left(\frac{4Dt}{\pi h^2}\right)^{1/2} \quad \text{For } 0 \leq \text{Mt/Mo} \leq 0.6 \qquad \text{Equation 5.4}$$

The late time approximation, which holds for the latter portion of the drug release, is given by equation 5.5.

$$Mt / Mo = 1 - \left(\frac{8}{\pi^2}\right) \exp\left(-\pi D t h^2\right) \quad \text{For } 0.4 \leq \text{Mt/Mo} \leq 1.0 \qquad \text{Equation 5.5}$$

Where Mt = amount of drug released in time, t

Mo = total mass of drug loaded into the hydrogel

D = diffusion co-efficient of the drug

h = thickness of hydrogel

Differentiating these equations with respect to time gives release rates at any particular time.

$$\frac{dM_t}{dt} = 2M_o\left(\frac{D}{\pi h^2 t}\right)^{1/2} \qquad \text{For } 0 \leq \text{Mt/Mo} \leq 0.6 \qquad \text{Equation 5.6}$$

$$\frac{dM_t}{dt} = \left(\frac{8DM_o}{h^2}\right)\exp\left(\frac{-\pi^2 Dt}{h^2}\right) \qquad \text{For } 0.4 \leq \text{Mt/Mo} \leq 1.0 \qquad \text{Equation 5.7}$$

These equations can be used to model expected release rates from hydrogels for which the diffusion co-efficient of a drug has been experimentally established.

This type of behaviour has not previously been investigated in hydrogel systems where the nature of the polymer and the component released have been independently varied. The observed behaviour summarised in the semi-log plot shown in figure 5.15 is qualitatively consistent with release kinetics that have been observed in other systems and analysed in terms of the two Crank expressions (which are valid for different parts of the release profile).

In the present systems the initial burst release appears to occupy between 20% and 90% and the second phase, that is the first order phase, can be between 10% and 65%. The first phase of release is so variable depending on the polymer, the drug and the extractant. This work concentrated on the ability to manipulate release profiles post-initial burst. As the researcher wished results for the second stage of release to be comparable it was important to ensure that the extraction solution had equilibrated with the contact lens (i.e. the contact lens was hydrated to its normal size) prior to measurements of release. This was achieved by rinsing the loaded contact lenses to remove surface contaminants and soaking them in distilled water until they reached their original size (5-15 minutes). For some contact lenses, in particular, low water content, neutral lenses, this initial burst equilibrium acted as a very effective extraction, resulting in very rapid removal of the loaded compound available at the release surface and a greatly reduced the experimental burst phase of release.

This release work has demonstrated that there are a variety of controlling mechanisms for release from hydrogels which work together to determine the release profile of a compound from a particular hydrogel composition into the external environment. Key factors controlling release are drug ionisation, polymer/water components of the hydrogel, and the characteristics of the external release medium. Interaction of these parameters determines the rate of release of a compound from the hydrogel.

The concentration of model compound initially loaded into a hydrogel alters the amount released during each of the three phases of release. Up to the point at which diffusion of the compound through the hydrogel becomes the limiting factor to release an increase in initial loading concentration will increase the rate at which the compound can be released into the external medium. Above this point diffusion of the compound through the material will prevent any increase in delivery rate with increased loading concentrations. The effect of initial loading concentration is most evident in the initial burst phase of release. Here, greater availability of the compound in the portion of the hydrogel adjacent to the release surface results in a dramatic increase in the extent of release in this phase from hydrogels with greater initial loading concentrations. As this portion of the hydrogel is depleted of the compound release becomes dependent on diffusion of the compound through the hydrogel to the release surface.

The balance of hydrophobic and hydrophilic components of a release system presented by the polymer, drug and external environment give an immense amount of control over release of a compound, in particular the steady state phase of release. Release behaviour is not a simple process and cannot be explained fully. For example, it is uncertain whether release into octanol continues infinitely at an infinitesimal rate. Though release cannot be predicted absolutely, patterns of release behaviour can be used to anticipate vehicle requirements for desired release rates to be achieved for a drug.

The relative hydrophilicity of a compound, quantified by its diffusion coefficient, determines its partition between the polymeric delivery vehicle and the external release environment. More hydrophobic compounds will partition more favourably into the more hydrophilic environment, be that the hydrogel or the external release environment. Likewise, more hydrophobic compounds will partition most favourably into the more lipophilic environment. The diffusion coefficient of the release compound must be

considered in conjunction with the nature of the hydrogel polymer backbone and the release medium. Indeed, conventional gel-forming polymers used in pharmaceutics often have more negative $K_{o/w}$ values than the monomers used here, for example, hydroxyethyl cellulose; $K_{o/w}$ = -5.5 compared to vinyl pyrrolidone; $K_{o/w}$ = 0.38, AMO; $K_{o/w}$ = -0.37). Although $K_{o/w}$ is a very useful indicator, it always deals with the neutral situation (it relates to molecules in their unionised form) so when dealing with molecules in their ionised form and acid-base/anion-cation/polar-polar interactions to different extents, the situation becomes more complex than $K_{o/w}$ values are able to deal with.

Interactions between the release compound and the polymer backbone of the hydrogel will reduce the amount of compound available for release. Changes to water content of the hydrogel and the nature of its constituent monomers influence the degree of affinity of the compound for the hydrogel material in preference to the external environment.

Ionisation-state of a drug at the time of loading and any changes that occur as a result of the pH at the release surface, determine the proportions of ionised and non-ionised drug available for release. Diffusion co-efficients of both forms of the drug and the polymer control the partitioning of the compound between aqueous and polymeric components of the hydrogel. The nature of the external environment in terms of its pH and its lipophilicity subsequently determine partitioning of a compound between the release vehicle and the external environment.

Chapter 6

Loading and release from partially hydrated ionic hydrogels

6. Loading and release from partially hydrated ionic hydrogels

6.1 Introduction

Having identified and understood the factors within a hydrogel release system that influence release of model compounds, similar studies of release of biologically active compounds were carried out. Study compounds were chosen on the basis of their solubility and provision of therapeutic benefit through topical/transdermal application.

Effective delivery of active compounds from a delivery vehicle to the skin depends not only on both the release rate of the compounds but also on localisation of release at the delivery site. Intimate skin contact by the delivery device and prolonged delivery times are important in ensuring optimum dosage of a drug.

The partially hydrated hydrogel compositions developed during the earlier stages of this research programme can be employed as delivery vehicles whose inherent skin adhesive properties allow long-term intimate skin contact. The composition of these materials has been shown to influence hydrogel adhesivity and associated skin adhesion. As with fully hydrated hydrogels, further manipulation of composition can be used to control release of loaded compounds from the hydrogels. This chapter of work looks at the loading and release behaviour of typical partially hydrated ionic hydrogels.

One advantage of fully hydrated hydrogels is that these materials can be placed in a surrounding fluid and release can be studied in the knowledge that the level of hydration of the hydrogel will change very little if at all. A problem encountered when studying release from partially hydrated adhesive hydrogels is that the act of putting the material into fluid to allow release of a loaded active is accompanied by uptake of this fluid by the hydrogel. This alters the structure and composition of the material and also makes measurement of the release of the active into the external reservoir of fluid extremely difficult as its volume is continuously changing. These competing transport gradients of release of the active out of the hydrogel and uptake of release medium into the hydrogel lead to a degree of complexity that is difficult to analyse. In practical terms the obvious

way forwards is to undertake a series of release experiments, study the results and attempt to interpret them.

6.2 Entrapment of compounds within partially hydrated hydrogels

Partially hydrated hydrogels differ from conventional fully hydrated hydrogels in their method of synthesis. Unlike fully hydrated hydrogels that are swollen to equilibrium after polymerisation this class of hydrogels are polymerised in the presence of a pre-determined amount of water below the EWC of the gel. In order to maintain the pre-determined water content of these materials, release compounds must be entrapped within the hydrogel during polymerisation rather than being loaded in solution into a pre-prepared material. Incorporation of actives in this way is much simpler and more controlled but brings with it the issue of potential effects of the polymerisation process on the compound and potential detriment to its therapeutic activity. Choice of active compounds and initial loading concentrations must take this possibility into consideration.

When the hydrogel is placed in an environment which causes it to swell the mesh size of the hydrogel network increases allowing release of the compound. The compound will now partition between the hydrogel and the external environment to the point of equilibrium. Swelling of the hydrogel can be induced by changes in environmental pH, temperature or ionic strength.

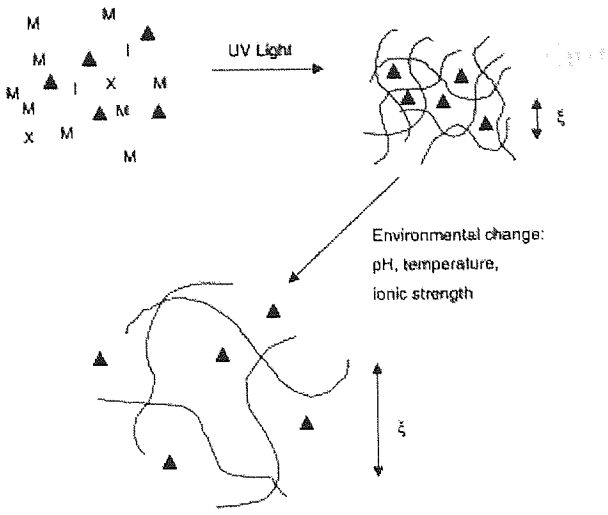


Figure 6.1 Photopolymerisation of a hydrogel in the presence of a biomolecule (σ) and subsequent swelling in response to a change in the environment.

Here, M is monomer, X is crosslinker, I is initiator and ξ is the mesh size (Ward & Peppas, 2001)

6.3 The effect of hydrogel hydrophilicity on solute affinity

If partially hydrated hydrogels are to be effectively employed in the controlled release of active compounds, the effects of the unique properties of these materials on release must be identified. Previous work allows the researcher to predict that changing from a neutral to an ionic release vehicle will alter the affinity of a compound for the hydrogel and its subsequent release rates.

Dissolved or dispersed active compounds diffuse through a hydrogel within the free water in the material. During hydration of a hydrogel water primarily binds to any hydrophilic polar groups within the polymer. As the hydrogel swells and the polymer chains expose their hydrophobic groups these too become hydrated. The final stage of hydration is the swelling of the hydrogel network with free water up until the point where elastic refraction forces limit further uptake of water. The total amount of water within the hydrogel at this point is known as its equilibrium water content. In the case of partially hydrated hydrogels this limit is not reached and the amount of free water within the hydrogel is decreased. This may limit diffusion of solutes through the hydrogel, reducing release rates.

The presence of ionic groups within the polymer backbone provides a more hydrophilic, water-like environment within these partially hydrated hydrogel compositions than the environment within the neural hydrogels previously studied. This will affect partitioning of loaded compounds between the aqueous and polymeric components of the hydrogel and between the hydrogel and the external release environment. Release into aqueous media in particular will be much less influenced by the polymeric component of the hydrogel as a result.

6.4 Aims of this chapter

Topical delivery of biologically active compounds avoids problems encountered by first pass metabolism of orally administered systemic drugs and provides an attractive means of delivery of many pharmaceutical and cosmeceutical compounds.

In order that therapeutically effective concentrations of a topically applied drug are available at a release site the drug should ideally be released at a constant rate equal to its absorption into the skin. The burst phase of release from hydrogels, demonstrated previously, provides an initial reservoir of drug at the application site which will be replenished by the second, first-order, phase of release. This profile of release is ideal for topical application of cosmeceuticals and acute therapies such as localised pain relief.

Partially hydrated skin adhesive hydrogels provide a means of applying and delivering active compounds within the same system eliminating manufacturing complexities encountered with multi-component controlled delivery devices. Having previously examined the scope for manipulation of the adhesive and handling properties of this class of hydrogels to suit dermal application, drug release properties of these compositions will now be assessed.

Work discussed in chapter 5 of this thesis confirmed the importance of the diffusion coefficient of a compound on its rate of release into media of different hydrophilicities. The affinity of ionised and unionised forms of a compound for the hydrogel was important in determining its partitioning between the hydrogel delivery vehicle and the external release medium. Interactions between the hydrophobic polymer backbone of neutral hydrogels and the unionised form of a model compound were shown to limit release.

This chapter investigates the effect of the presence of charged groups within the polymer backbone. Interactions between the ionic groups of the constituent monomers of the partially hydrated hydrogels and loaded compounds will differ to those observed with neutral hydrogels. Polar, ionic forms of a compound will have greater affinity for the polymer backbone of the hydrogels.

The effect of reduced water content on release characteristics will also be examined to establish to what degree the reduction of free water for diffusion of solutes affects release.

The chapter aims to study two aspects of release from partially hydrated hydrogels:

- in vitro release profiles of study compounds
- release onto the skin

It must be acknowledged that swell of the hydrogel samples with water during release experiments will be a factor in aqueous release profiles. More specifically, imbibition of aqueous release medium into the hydrogel will alter the pH within the material, affecting the degree of ionisation of the loaded compound.

Studies will model release conditions at the skin surface for this mechanism of release (i.e. constant water content, low water content hydrogel) in which release from the aqueous phase may be delayed by partitioning of the drug between the hydrogel and the water (both are hydrophilic and ionic). In choosing a reasonable model the suitability of a fully hydrated version of the partially hydrated adhesive hydrogel was considered. However, the amount of water and glycerol within the hydrogel and the nature of the polymer backbone are all important in influencing release and the greatly reduced amount of free water available in partially hydrated hydrogel makes the materials incomparable.

Loading and release of some biologically active compounds will be studied including ibuprofen, a non-steroidal anti-inflammatory drug already used in topical ointment formulations. The kinetic release profiles of fluorescein observed in the previous chapter of this thesis are anticipated to provide a useful model of the release behaviour of this molecule.

6.5 Partially hydrated ionic hydrogel compositions

Partially hydrated ionic hydrogels characterised in chapter 4 of this thesis were used in these release studies. Chosen compositions had demonstrated good adhesive and cohesive characteristics and represent a range of release conditions. Table 6.1 below gives composition details for the hydrogels.

Composition name	Composition (%) *	
SN6.4/35	monomer *(SPA:NaAMPS, 6:4)*	40
	glycerol	25
	water	35
SN6.4/25	monomer *(SPA:NaAMPS, 6:4)*	50
	glycerol	25
	water	25
SPA/35	SPA	40
	glycerol	25
	water	35
NaAMPS/35	NaAMPS	40
	glycerol	25
	water	35
Commercial hydrogel	NaAMPS	37
	propane diol	15
	water	48

Table 6.1 partially hydrated ionic hydrogel compositions

All hydrogel compositions were crosslinked with 1% Ebacryl:Irgacure 184 (10:1) crosslinker:initiator mix with the exception of the commercial composition in which 0.24% of an unknown crosslinker was used.

*Percentages given are for individual components, actual measurements included compensation factors for NaAMPS which was purchased as a 58% aqueous solution.

6.6 Models

6.6.1 Photopolymerisation of partially hydrated ionic hydrogels in the presence of a dye model

The absorbance of the dye models studied in chapter 5 occurs at a much greater wavelength than that of ultra violet light. Loading of partially hydrated hydrogels with the model compounds at high concentrations was anticipated to be problematic for the photopolymerisation method used the production of partially hydrated hydrogels. A range of concentrations of the models were photopolymerised into a skin adhesive hydrogel composition to determine whether low concentrations of the compounds could in fact be loaded into the hydrogels and used in release studies, allowing comparison of the release profiles of the compounds from fully and partially hydrated hydrogels.

A skin adhesive composition shown previously to demonstrate good mechanical and adhesive properties following rapid photopolymerisation (SN6.4/1) was polymerised in the presence of a range of concentrations (0.01% - 1.0%) of BPR and a standard concentration (0.33%) of 1:10 Igracure:Ebacryl mix (see appendix I). Samples were prepared as described in section 2.3.2, with addition of dye and overnight mixing of the sample prior to addition of the initiator/crosslinker mixture. Polymerisation of the samples on lined trays using a GEW 310 UV lamp proved successful only for those samples containing low concentrations of the dye, as shown in table 6.2.

Concentration bromopyrogallol red	Number of passes through UV source	State of polymerisation
0.01%	4	Fully polymerised hydrogel
0.1%	10	Fully polymerised hydrogel but dye leaching
0.5%	10	Polymerisation incomplete
1.0%	25	Polymerisation incomplete

Table 6.2 photopolymerisation in the presence of bromopyrogallol red

Higher concentrations of BPR (0.5% and 1.0%) within the range investigated prevented photopolymerisation of the samples most probably by blocking absorption of UV light in the deeper layers of the sample and so preventing initiation of polymerisation. Levels of 0.1% and below allowed transfer of the UV light through the sample and gels were produced within reasonable time frames. Transfer of dye onto the release paper from the sample containing 0.1% BPR may have been due to saturation of the gel with dye or due to poor entrapment of the dye within the hydrogel network at these levels of crosslink density. Leaching of the dye in this way leads to ambiguity regarding actual concentrations loaded and the presence of a precipitate at the hydrogel surface compromises its adhesive properties. Increased concentrations of photoinitiator may enable higher concentrations of the compound to be loaded into skin adhesive hydrogels but would reduce chain length, altering the mechanical characteristics of the hydrogel.

The absorbance wave lengths of sodium fluorescein and fluorescein are also significantly higher than the wavelength of UV light and can be expected to hinder photopolymerisation in a similar manner. As partially hydrated hydrogels must be polymerised in the presence of the release compound dyes were deemed unsuitable for use as model compounds for measuring release from these hydrogels. Work now focussed on the loading and release of useful biologically active compounds.

6.7 Topical delivery of antioxidants

The skin is frequently exposed to oxidative attack from external sources of oxidising agents including ultraviolet radiation, drugs and air pollution as well as those continuously produced during physiological cellular metabolism (Thiele et al, 2000). Free radicals produced by these reactive oxygen species oxidise lipids in the skin and breakdown enzymes and matrix proteins leading to anatomical changes such as thinning of the epidermis, thickening of the stratum corneum, loss of collagen and increased appearance of lines and wrinkles.

Antioxidant systems within the skin maintain the balance between prooxidants and antioxidants in the skin so that oxidative damage to the skin structure is minimised. Some antioxidants, such as glutathione and ubiquinol-10, can be synthesised by humans as required but others, including vitamins C and E, have to be supplied from external sources (Thiele et al, 2000).

Excessive exposure to reactive oxygen species e.g. prolonged from exposure to UV, can overwhelm the skin antioxidant mechanisms of the skin resulting in premature signs of ageing. Topical application of exogenous antioxidants such as vitamins C and E provides a means of increasing antioxidant levels in the skin to minimise the harmful effects of exposure prooxidative environments.

6.7.1 Topical delivery of ascorbic acid (Vitamin C)

Ascorbic acid can prevent oxidative damage by deactivating oxidative free radicals, and has been shown to be used in free radical chain oxidation during skin exposure to ultraviolet light (Yamamoto, 2001). It can also stimulate collagen synthesis through the hydration of the proline and lysine residues of procollagen, promoting conformation of the triple-helix of mature collagen fibres (Zhang et al, 1999). It has also been used as a skin lightening agent in areas of high pigmentation.

Topical delivery of ascorbic acid allows levels of the compound to be reached in the skin which are not possible by its consumption in food or as an oral supplement. Skin adhesive hydrogels present an ideal means of sustained delivery directly to the skin. Ascorbic acid is a water-soluble anti-oxidant and as such will be readily dissolved in the water within the hydrogel network. The high initial burst release of hydrophilic compounds from fully hydrated hydrogels that was demonstrated in previous results is likely to be seen again with partially hydrated hydrogels. The increase in hydrophilicity of these hydrogels due to the presence of anionic groups on the hydrophilic constituent monomers will allow much higher loading concentrations to be achieved with relative ease. The low affinity of the compound for the polymeric component of the hydrogel will make release of the compound almost solely diffusion controlled in the absence of an external control such as a membrane.

As an anti-oxidant, ascorbic acid is vulnerable to oxidation during exposure to ultraviolet light during photopolymerisation and active concentrations may be severely depleted. Roche have developed a stable version of the compound, STAY-C® 50. The active centre of this molecule is temporarily blocked and is biologically activated by phosphatase, a normal constituent of skin. For financial reasons vitamin C was used in this work however, in the case of development of a successful controlled release system this could be replaced with the STAY-C® 50 compound.

6.7.2 Topical delivery of tocopherol (Vitamin E)

Vitamin E is the major lipophilic antioxidant that acts as an antioxidant by scavenging lipophilic free radicals. Its presence also enables ascorbate to reduce lipid peroxyl radicals by reacting with tocopheroxyl radicals. The lipophilicity of the compound means that it is easily absorbed into skin but will hinder its incorporation into a hydrophilic polymer. It is likely to be more readily incorporated into polymers with hydrophobic backbones but interactions between the compound and the polymer may result in high levels of unrecovered compound remaining within the polymer. Bi-phasic hydrogels, which combine hydrophilic and hydrophobic components as separate phases within the same material, may provide a means of achieving topical delivery of vitamin E from hydrogels. A hydrophobic component would allow therapeutically active concentrations to be loaded into the hydrogel whilst a hydrophilic component would produce more favourable partitioning of the compound between the hydrogel and the lipoidal environment of the skin. Studies of release from bi-phasic hydrogels are beyond the scope of this thesis however, and as such, vitamin E was not studied further during this program of research.

6.7.3 Loading of partially hydrated hydrogels with ascorbic acid

6.7.3.1 Photopolymerisation in the presence of ascorbic acid

Samples (50g) of a successful skin adhesive hydrogel composition (SN6.4/35, see section 6.5) were loaded with increasing concentrations of ascorbic acid (vitamin C) prior to photopolymerisation. Monomer/glycerol /water mixtures were measured into vessels and mixed thoroughly prior to the addition of ascorbic acid, again followed by thorough mixing of the sample before addition of 0.33% (0.165g) of standard 1:10 initiator:crosslinker mix. Samples were shaken and spread onto a tray lined with release paper. Descriptions of the resultant gels were noted in table 6.3.

Concentration ascorbic acid	pH of sample	Description of hydrogel
0.001%	5.79	Cohesive, adhesive, good handling characteristics
0.01%	5.74	Cohesive but brittle, less adhesive, good handling characteristics
0.10%	5.59	Cohesive, adhesive, good handling characteristics
1.00%	5.53	Very tacky, wet, non-cohesive, incomplete polymerisation
5.00%	4.12	Very tacky, wet, non-cohesive, incomplete polymerisation
10.00%	3.73	Required addition of 1 drop sodium hydroxide (volumetric standard) to aid dissolution. Failed to polymerise.

Table 6.3 Entrapment of increasing concentrations of ascorbic acid within a partially hydrated hydrogel

Low concentrations (up to 0.1%) of ascorbic acid were readily entrapped within the partially hydrated hydrogel by photopolymerisation. The hydrogels produced were fully polymerised to produce adhesive hydrogels with good handling characteristics.

The presence of ascorbic acid at concentrations of 1% and above prevented complete polymerisation of the samples. Polymerisation is hindered in the presence of the higher concentrations of ascorbic acid by the anti-oxidant behaviour of the compound. The ascorbic acid molecules scavenge photoinitiator free radicals that are essential for chain propagation. As a result of premature completion of the polymerisation reaction, polymer chains are short and unpolymerised monomer remains.

The pH of the composition decreased with increasing concentrations of ascorbic acid. Decreased solubility of ascorbic acid at low pH meant that high concentrations (10%) of ascorbic acid were insoluble in the composition. Sodium hydroxide was added to the monomer solution to increase pH so that the compound could be fully dissolved prior to entrapment within the hydrogel.

It is desirable that higher concentrations of ascorbic acid are successfully entrapped within the hydrogel delivery system if therapeutically effective dosage is to be achieved. An increase in initiator concentration to counteract the scavenging of free radicals by the ascorbic acid is associated with changes to the mechanical properties of the hydrogel. The use of oxidising agents to "mop up" atmospheric oxygen at the surface of the hydrogel will be explored.

6.7.3.2 Photopolymerisation in the presence of ascorbic acid plus redox systems

The principle of redox polymerisation of water-soluble species is typified by the behaviour of Fenton's reagent.

$$Fe^{++} + H_2O_2 \rightarrow Fe^{+++} + OH^- + \bullet OH$$

Reducing agent — Oxidising agent

Fe^{++} is itself oxidised, whilst H_2O_2 is reduced. •OH acts as a water-soluble initiator of free radical polymerisation. There are however lots of other methods of redox polymerisation.

Other redox pairs include:

- Ascorbic acid and potassium oxypersulphide
- Metabisulphate – a reducing agent that can use O_2 and interact with photoinitiators.

As a means of overcoming the antioxidant effects of ascorbic acid experienced in photopolymerisation of partially hydrated hydrogel compositions in the presence of ascorbic acid, redox systems were added to the samples. Samples (50g) of monomer/glycerol/water were prepared according to composition SN6.4/35 (see appendix I). Low concentrations (1% and 0.5%) of sodium metabisulphite (sacrificial reducing agent) and sodium persulphate (redox pair with ascorbic acid) were added and samples shaken well. Standard concentrations (0.33%) of 1:10 initiator/crosslinker mix were then added to the samples, which were then polymerised with a GEW 310 UV lamp (see section 2.3.2). Descriptions of the resultant gels were noted.

Concentration ascorbic acid	**Concentration sodium persulphate**	**Concentration sodium metabisulphite**	**Description of hydrogel**
0.5%	0.0%	0.5%	failed to polymerise
0.5%	0.5%	0.0%	failed to polymerise
1.0%	0.0%	1.0%	cohesive, adhesive, good handling characteristics
1.0%	1.0%	0.0%	partially polymerised during O/N shaking

Table 6.4 Entrapment of increasing concentrations of ascorbic acid within a partially hydrated hydrogel in the presence of redox agents

The use of redox initiator systems proved only partially successful in assisting polymerisation of the hydrogels in the presence of ascorbic acid. The redox initiators were added at concentrations to match those of the incorporated ascorbic acid. Sodium

persulphate proved unsuitable for use in these systems. At a concentration of just 1.0% its oxidising effect during polymerisation was sufficient to promote polymerisation of samples during overnight mixing. This was avoided by use of lower concentrations of the compound however the observed reduction in the solubility of the vitamin may prevent loading of the high concentrations desirable in cosmetic applications of the compound. Sodium metabisulphite demonstrated potential for use as a sacrificial reducing agent to promote polymerisation in the presence of ascorbic acid. Use of the initiator at 1.0% produced adhesive hydrogels with good handling characteristics.

Ward and Peppas (2001) investigated the effect of solute on polymerisation and synthesis of a hydrogel release device. They developed a kinetic gelation model and used this to examine network formation during polymerisation. They determined that the presence of a solute during polymerisation would result in greater numbers of microgel regions, a more heterogeneous material and a delay in gel point. Kinetic experiments agreed that the presence of a low molecular weight solute increased polymerisation rates of short-chain monomers because functional groups were in closer proximity to each other. Longer chain monomers were not as greatly affected due to the wider spacing of functional groups by the chains.

6.8 Topical delivery of ibuprofen

Ibuprofen belongs to the family of non-steroidal anti-inflammatory drugs widely used in the treatment of arthropathies because of their potent anti-inflammatory and analgesic activity. The drug is conventionally administered orally but this is frequently associated with gastric irritation and contraindicates its use by many patients. Topical application of the drug avoids this problem and any issues associated with first pass metabolism of the drug. Topical release of ibuprofen would be particularly useful in the treatment of muscle pain, soft tissue rheumatism and sports injuries. The drug could be applied specifically within a localised area rather than systemically to areas not requiring treatment.

Topical delivery of ibuprofen requires controlled and consistent release of the drug from a delivery vehicle to ensure that therapeutic levels are achieved without the risk of toxic effects of high concentrations of the drug. As demonstrated previously, diffusion co-efficients of a drug are important in influencing release of a drug from a delivery vehicle into the release environment. The effects of environmental conditions on the ionisation and partitioning behaviour of a drug, both from the delivery vehicle and across the skin, are important considerations in the development of a controlled delivery device.

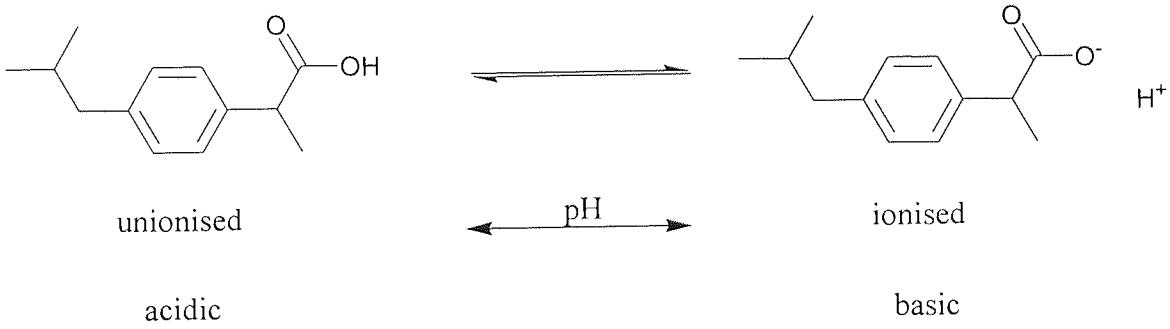


Figure 6.2 Structures of ionised and unionised forms of ibuprofen

Figure 6.3 shows the variation in diffusion coefficient of ibuprofen with pH. The pKa of ibuprofen has been documented at around pH 4.4 (Hadgraft & Valenta, 2000). Any

increase in pH above this will alter the distribution of ionised and unionised forms of the drug, which differ in their hydrophilicity and therapeutic viability. The degree of ionisation of the drug within a delivery device will alter the release characteristics for the system and will determine the suitability of the vehicle for topical delivery of ibuprofen

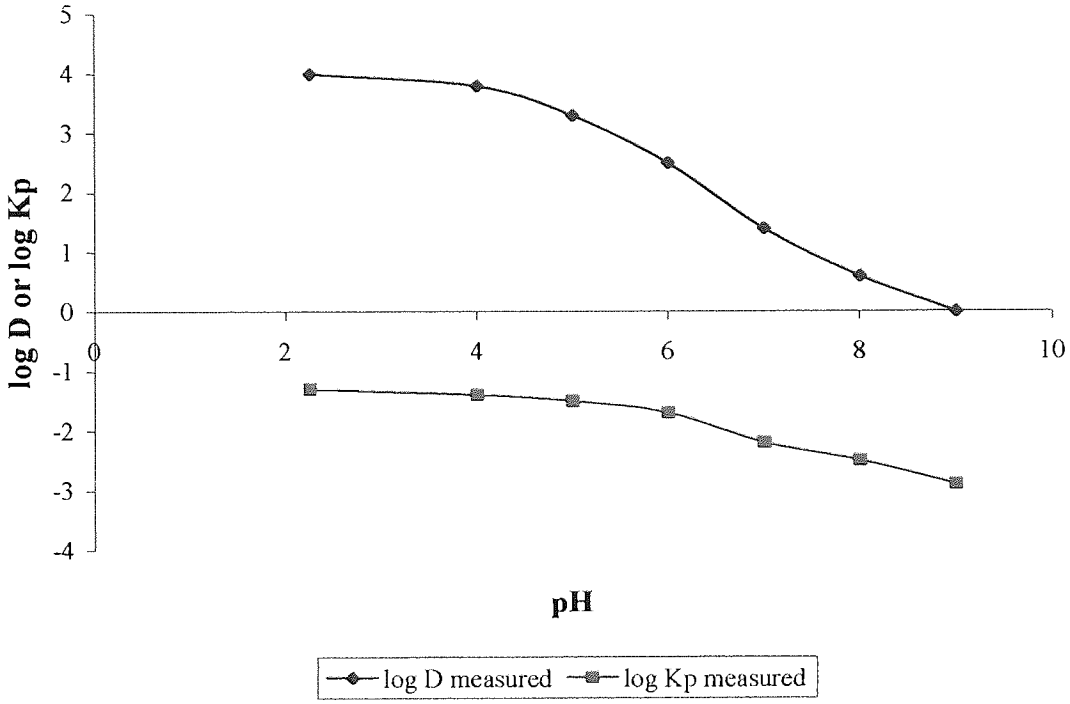


Figure 6.3 Variation in predicted (and measured) logD and log Kp of ibuprofen with pH
(Hadgraft & Valenta, 2000)

Watkinson et al (1993) measured the solubility of ibuprofen in water at different pH. Solubility was shown to decrease with increasing pH (Figure 6.4). The ionised form of ibuprofen (measured by Hadgraft and Valenta to have a more negative diffusion co-efficient than the unionised form) will be more soluble in the aqueous phase and the unionised form more soluble in the organic phase. Hence, an acidic pH will optimise the extraction of the acid into organic solvent and a basic pH will optimise the extraction of the base into an aqueous media. This effect is known as ion suppression.

pH	2.2	2.3	4.0	5.0	6.0	7.0	9.0	9.2
Solubility (mg/ml)	0.024	0.027	0.029	0.096	0.52	3.70	7.83	14.8
Permeability co-efficient (cm/h)	0.06	0.053	0.045	0.036	0.019	0.0066	0.0024	0.0012

Figure 6.4 Solubility and permeability properties of ibuprofen as a function of pH *(Watkinson et al, 1993)*

6.8.1 Loading of partially hydrated hydrogels with ibuprofen

Partially hydrated hydrogel compositions were loaded with ibuprofen by entrapment of the drug within the hydrogel network during photopolymerisation. Reduced volume (1g) samples of partially hydrated hydrogel compositions were prepared. To these 2.5% w/w ibuprofen (acid) dissolved in a small volume of methanol was added. Samples were polymerised according to the moving web method 2.3.2 in the presence of 1% Ebacryl ll/Irgacure 184 (10:1) mixture.

6.8.2 In vitro release of ibuprofen

Release from partially hydrated hydrogels was studied using a vertical diffusion cell system. This allowed separation of the hydrogel from the release medium by a membrane to prevent excess swelling of the hydrogel by the release media. The membrane also acts as a support to the sample, positioning it directly over the release medium.

Samples of ibuprofen-loaded hydrogels were loaded into the diffusion cells as described in section 2.5.2. GN6-metricel pre-cut membrane filter discs with 45μm pore size were used to support the hydrogel samples directly above the release media without limiting diffusion of the loaded species (Ibuprofen molecular weight = 206.3). Experiments were carried out at laboratory temperatures that ranged from 14-18°C.

6.8.3 Measurement of release using High Performance Liquid Chromatography

Receptor media samples were analysed and quantified using isocratic reverse phase HPLC (section 2.5.3). Calibration curves were constructed for external standards of ibuprofen. Serial dilution (1/10) of a 0.1% stock solution of ibuprofen in mobile phase were used to prepare three standard concentrations. Standards were quantified in duplicate and plotted as a calibration curve (see appendix IV). Elution of ibuprofen occurred at around 10 minutes.

Samples (100µl) were filtered using 13mm, 0.45µm nylon filter units prior to injection into a 7125-rheodyne-injection system set to the load position. Excess sample is passed into the loop and flows into a waste overflow behind the 20µl rheodyne loop. Injection of excess sample in this way ensures that all liquid within the loop is from the current sample being analysed when the rheodyne is moved to the inject position. Both injection syringe and rheodyne loop were washed thoroughly with mobile phase between each sample to prevent cross contamination.

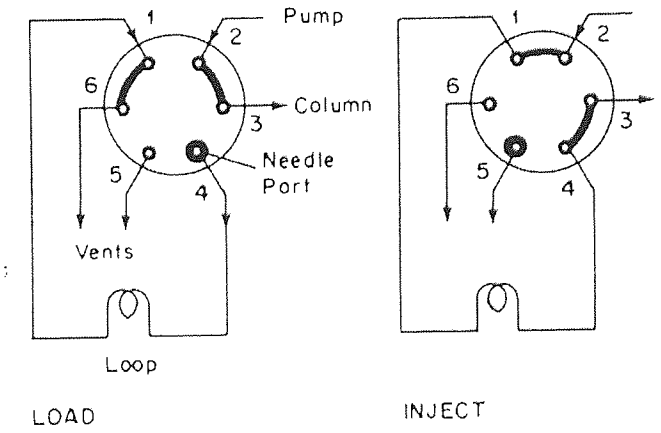


Figure 6.5 Flow diagram for a Rheodyne 7125 valve
(Lindsay, 1987)

Mobile phase was passed through a filter before reaching the column to remove any impurities that might jeopardise column efficiency. An internal sparging system within the Variant solvent delivery system degasses the mobile phase to ensure that air bubble from the mobile phase reservoir do not interfere with detection of sample components.

Starting point experimental conditions were sourced from a previous study by Snyder et al in 1988. The addition of one part to 100 phosphoric acid (H_3PO_4) was used to lower the pH of the mobile phase to around pH2 to ensure all ibuprofen (pKa 4) passing through the column was in its non-ionised form.

Experimental Conditions

Mobile phase: MeCN:H2O:H_3PO_4 (50:50:1)
Wavelength: 225nm
Flowrate: 1.0ml min^{-1}
Runtime: 14 minutes (elution of ibuprofen at around 11 minutes)
Column: Discovery RP Amide C16 5µm, 15cm x 4.6mm
(16-carbon hexadecyl ligand in matrix. Silica based packing with covalently bound n-alkyl chains)
Sample vol: 20µl
Temperature: ambient

HPLC equipment:
Variant solvent delivery system 9010
Variant UV-VIS detector 9050
Trio integrator and Trivector T1051
7125 rheodyne injection system

6.9 HPLC method development

6.9.1 Co-elution of peaks

A test run using the initial experimental conditions described showed co-elution of peaks for ibuprofen and octanol (release medium) which made calculation of peak area and ibuprofen concentration impossible. Identities of peaks were confirmed by injection of octanol and ibuprofen samples that had similar elution times to those of the co-eluted peaks. Co-elution is likely to have occurred because of the similarly hydrophobic nature of octanol and the unionised form of ibuprofen. Figure 6.6 shows a typical chromatogram from the test run (release into octanol).

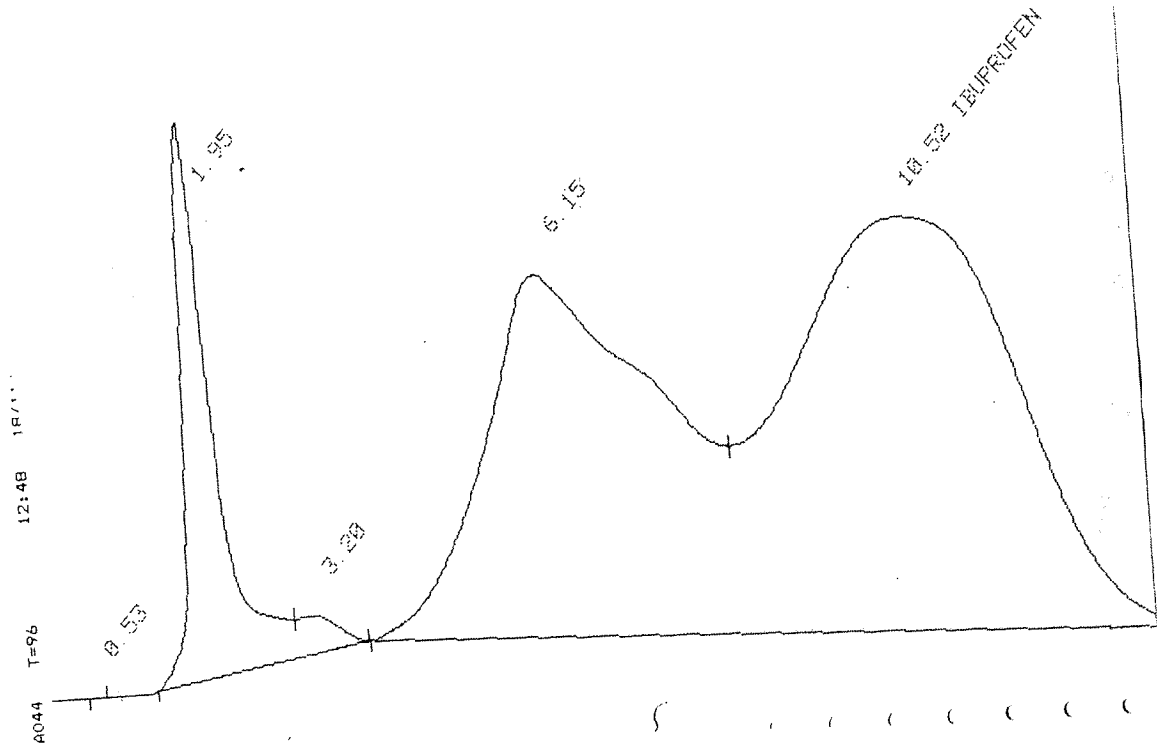


Figure 6.6 Chromatogram showing co-elution of peaks for Ibuprofen (10.52 mins) and octanol (6.15 mins)

HPLC method development was carried out in conjunction with Mr D Cambell

6.9.2 Alteration of flow rate

Attempts were made to separate the elution times of the two sample components by reducing the flow rate to 0.75ml min^{-1}. It was hoped that slowing flow of the sample through the column would allow time for increased interaction between ibuprofen and the column beads, shifting its elution time. Separation of the peaks was not achieved, they simply co-eluted at a later time. Further reducing the flow rate to 0.5ml min^{-1} extended retention time further but some overlap of peaks remained. Excessive run times made further reduction of flow rate impractical.

6.9.3 Alteration of mobile phase composition

Alteration of the hydrophilicity of the mobile phase affects interaction between the stationary and mobile phases, and as a consequence can change migration and separation rates. A more hydrophilic mobile phase composition (40:60:1) and a more hydrophobic composition (70:30:1) were tested. No improvement in peak separation was observed at the original flow rate of 1 ml min^{-1} or at higher and lower flow rates.

6.9.4 Dilution of sample

Differences between sample carrier medium and mobile phase composition can occasionally cause problems in HPLC analysis. Initial attempts to absolve this by 10-fold dilution of samples with mobile phase proved successful in reducing the octanol peak below minimal detection levels. Justification of results to compensate for the dilution subsequently proved the results to be inconsistent and unreliable.

6.9.5. Inclusion of additive in the mobile phase

Sharper peaks have previously been achieved by inclusion of competing acids within the mobile phase. Interaction of the acid with the silica hydroxyl groups of the column beads reduces similar interactions by the ibuprofen resulting in a more Gaussian elution of

ibuprofen. Neither addition of 1% acetic acid or 0.1% trifluoracetic acid (TFA) were successful under these experimental conditions.

6.9.6 Alternative mobile phase composition

An alternative mobile phase composition was sourced from industry (P B Healthcare). MeOH:H_2O:H_3PO_4 (750:247:3) was also unsuccessful in separating the peaks of octanol and ibuprofen.

6.9.7 Alternative organic release medium

Co-elution of octanol and mobile phase peaks was thought to be a result of immiscibility of the sample in the mobile phase. An alternative organic lipophilic release medium was introduced. Ethomeen solution is the recommended hydrophobic bridging solvent for saturation of membranes used with the Hanson vertical diffusion cell (Hanson Research, 2000). Elution of the solution was observed at around four minutes and injection of a 0.1% ibuprofen solution in the solvent produced two separate peaks at 8 and 4 minutes respectively.

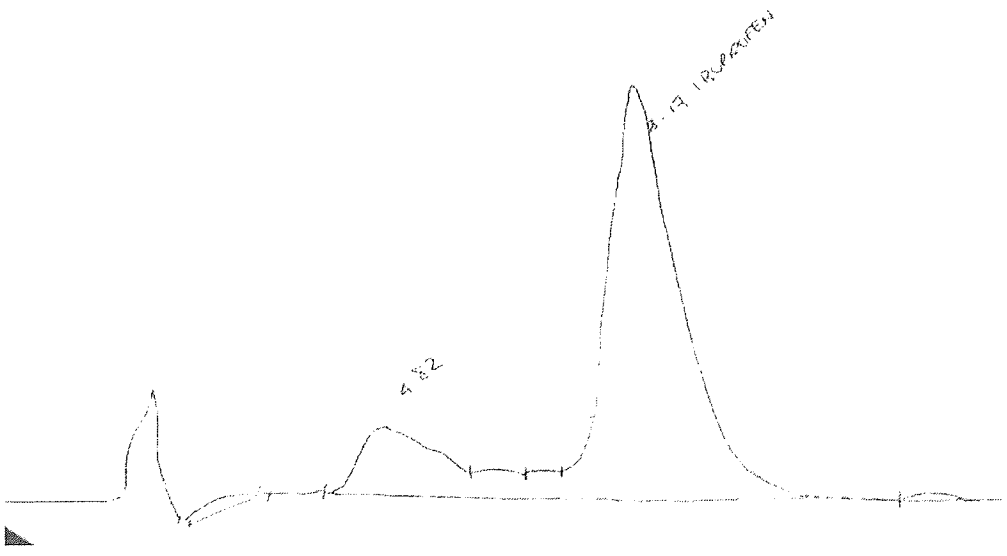


Figure 6.7 Chromatogram showing the separate elution of Ethomeen solution and octanol peaks

The successful elution of separate peaks for ibuprofen and Ethomeen solution led to Ethomeen being the choice of organic lipophilic medium for subsequent release studies.

6.10 Release of ibuprofen from partially hydrated hydrogels

6.10.1 Release of ibuprofen acid into aqueous and organic media from a typical partially hydrated hydrogel composition

Release of ibuprofen into aqueous and organic media was studied. A typical partially hydrated hydrogel composition, SN6.4/35 (composition details in section 6.5) was loaded with 2.5% ibuprofen acid, as described in section 6.8.1. Release of the drug from the hydrogel across a non rate-limiting membrane into Ethomeen solution (organic), phosphate buffered saline (pH7.4, aqueous) and pH4 buffer (aqueous) was measured. The effects of media influx into the hydrogel samples and subsequent effects on the ionisation of the loaded drug were studied with respect to their effects on release rates.

Figure 6.8 shows the cumulative release of ibuprofen into aqueous media of different pH over the first 48hrs of release. At this point in the release process the swell of the hydrogel sample with PBS ruptured the membrane separating the hydrogel sample from the release medium. The accompanying change in dimensions and water content of the hydrogel made further study of this release system impossible. Release into pH4 buffer was also associated with flux of the release medium into the hydrogel release vehicle. After only 5 hours of release the hydrogel had swollen with pH4 buffer sufficiently to rupture the GN6-Metricel membrane.

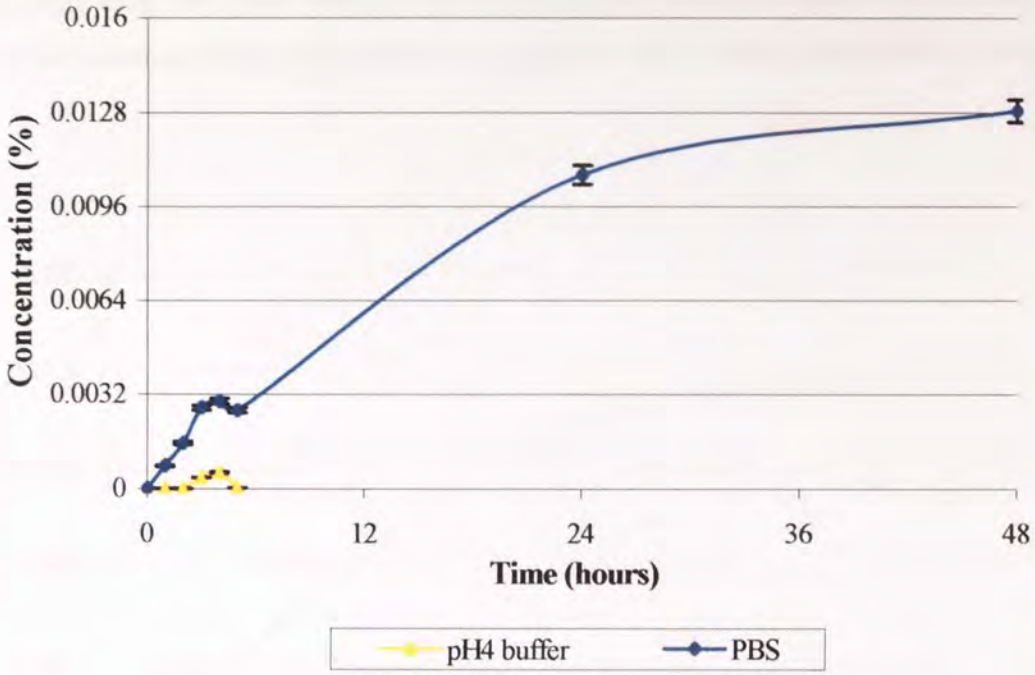


Figure 6.8 Cumulative release of ibuprofen from SN6.4/35 into aqueous media

Comparison of release into aqueous media at pH 4 and pH 7.4 demonstrated the effect of ionisation of ibuprofen on its release from the hydrogel into aqueous media. As described in section 6.8, the solubility (distribution coefficient) of ibuprofen varies with change in pH. The influx of PBS into the hydrogel, as demonstrated by the substantial swelling of the gel, increases the pH within the gel above the pKa of ibuprofen (around pH 4.4), resulting in the ionisation of a significant portion of the drug. Influx of pH4 buffer similarly alters the pH within the hydrogel. In this case however, equilibrium shifts towards the non-ionised form of the drug. As a consequence, the release of two species with different water/octanol partition coefficients is now being observed. The greater solubility of the ionised form of the drug in aqueous media as compared with the non-ionised form favours its release from the hydrogel into the aqueous medium, away from the proximity of the more hydrophobic polymer backbone. As a result the initial burst phase of release into PBS was much more rapid and extensive than that seen into pH4 buffer. Extended time release of ibuprofen into PBS was also significantly greater than the anticipated release into pH4 buffer. Interactions between the unionised ibuprofen and the polymer backbone of the pH4 release system along with the hydrophobic partitioning

nature of the drug limit partitioning of the drug into the aqueous medium. As such release rates of the unionised form of ibuprofen into aqueous media were significantly slower.

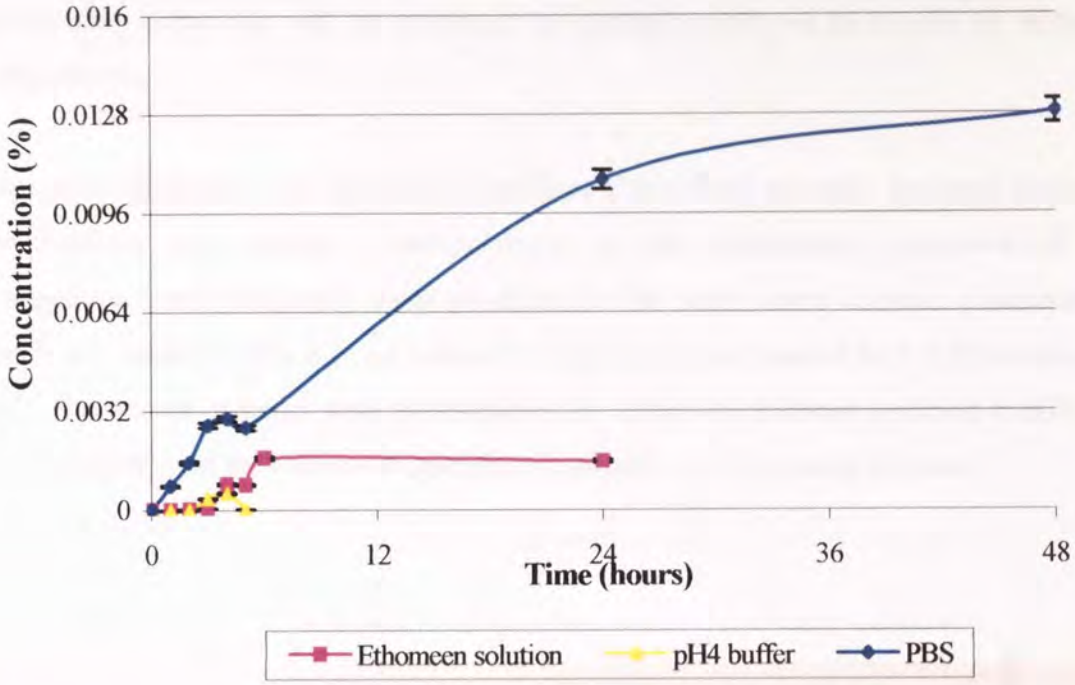


Figure 6.9 Cumulative release of ibuprofen from SN6.4/35 into aqueous and organic media

The effect of the hydrophilic/lipophilic nature of release medium on release can be seen by comparison of the release of ibuprofen into Ethomeen solution (lipophilic) and pH4 aqueous buffer (hydrophilic). In both systems all loaded ibuprofen will be in its non-ionised form (pH within hydrogel<pKa ibuprofen) allowing unambiguous comparison of the two media types.

Release into pH4 buffer was slower than release into Ethomeen for the first 5 hours of release however such limited results cannot be relied upon for detailed comparison of release into the two media. Theoretical reasoning does however suggest the apparent trend to be correct. The hydrophobic nature (positive water/octanol partition coefficient) of the unionised form of the drug will limit partitioning of the drug from the more lipophilic environment presented by the polymeric component of the hydrogel into the hydrophilic aqueous medium.

6.10.2 Release of ibuprofen into an organic release medium from three partially hydrated hydrogel compositions

Results in chapter five of this thesis have demonstrated the influence of hydrogel composition on the release behaviour of fully-hydrated materials. It is proposed that comparable behaviour will be exhibited by partially-hydrated hydrogels of differing compositions.

Release of ibuprofen into an organic medium from three partially hydrated hydrogel compositions was studied. Homopolymers of the constituent monomers of the composition used previously were produced at the same water content. Composition details are listed in table 6.1. As before the hydrogels were loaded with 2.5% ibuprofen acid. The release systems were investigated for effects of polymer partition coefficient (hydrophilicity) on the release of unionised ibuprofen into Ethomeen solution.

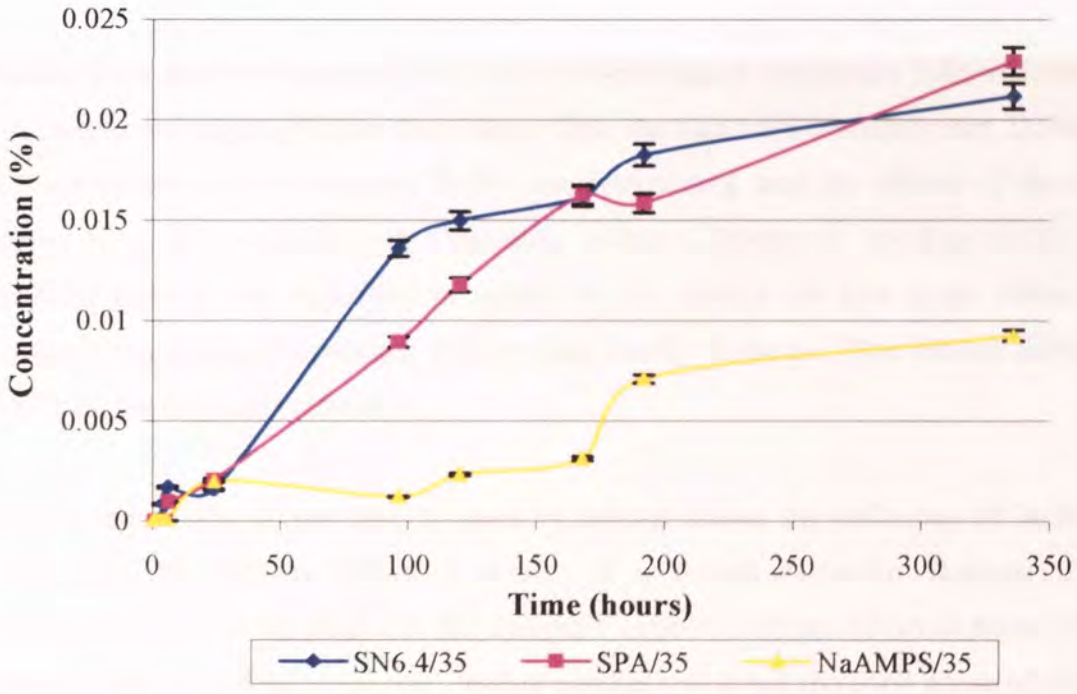


Figure 6.10 Cumulative release of ibuprofen from three hydrogel compositions into Ethomeen solution

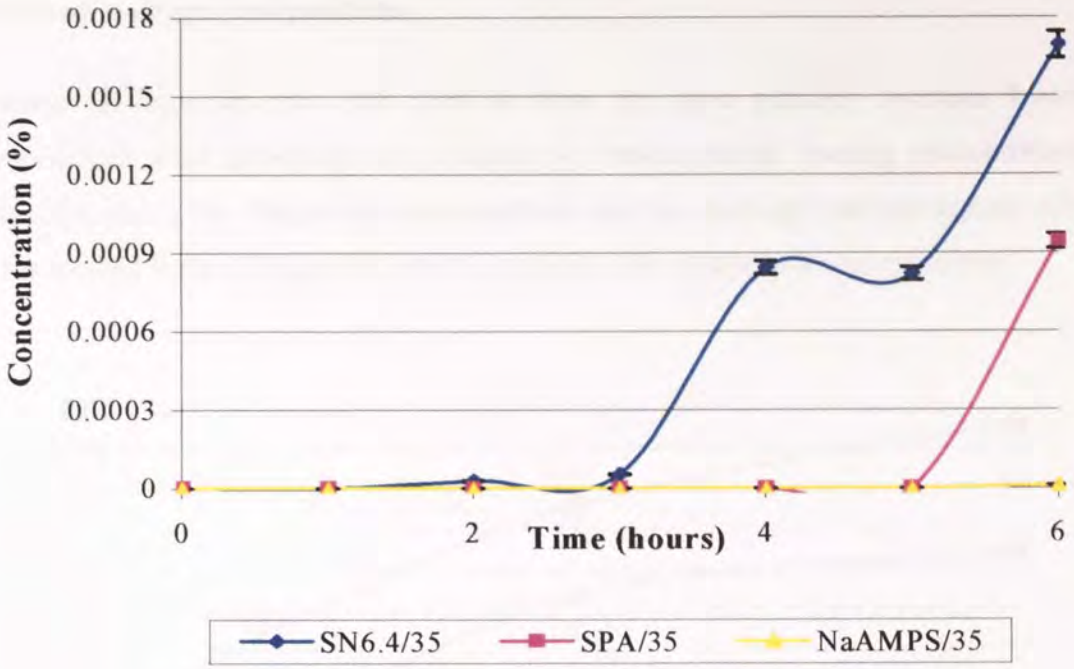


Figure 6.11 Cumulative release profiles for each of the systems during the first 6 hours of release

Release from the SPA homopolymer and SPA-dominated copolymer followed similar profiles and was slightly higher than release from the NaAMPS homopolymer. Diffusion of the drug through the polymer is the rate-determining step for release of the non-ionised form of ibuprofen into Ethomeen solution. Interchain bonding within the NaAMPS polymer (as described in section 4.5.6) reduces the free space within the hydrogel by effectively increasing the crosslink density of the gel. This hinders diffusion of solutes, limiting their release.

Closer examination of the first 6 hours of release shows the influence of hydrogel composition on the burst phase of release of unionised ibuprofen. Release of the hydrophobic form of the drug into the lipophilic organic medium occurred most rapidly from the SPA/NaAMPS copolymer. Within another two hours the burst phase of release from the SPA homopolymer had also begun. Release from the NaAMPS homopolymer was much slower, with no burst phase of release within the first 6 hours of release. The effective high crosslink density within the NaAMPS homopolymer slows diffusion of the ibuprofen resulting in the observed delay in release.

6.10.3 Release of ibuprofen into an aqueous release medium from three partially hydrated hydrogel compositions

Release of ibuprofen into PBS (pH7.4) from the three partially hydrated hydrogel compositions used previously was studied. As before, initial loading concentration of ibuprofen was 2.5%. Influx of release medium into the hydrogel and subsequent release of the ionised form of ibuprofen into the aqueous release medium was examined.

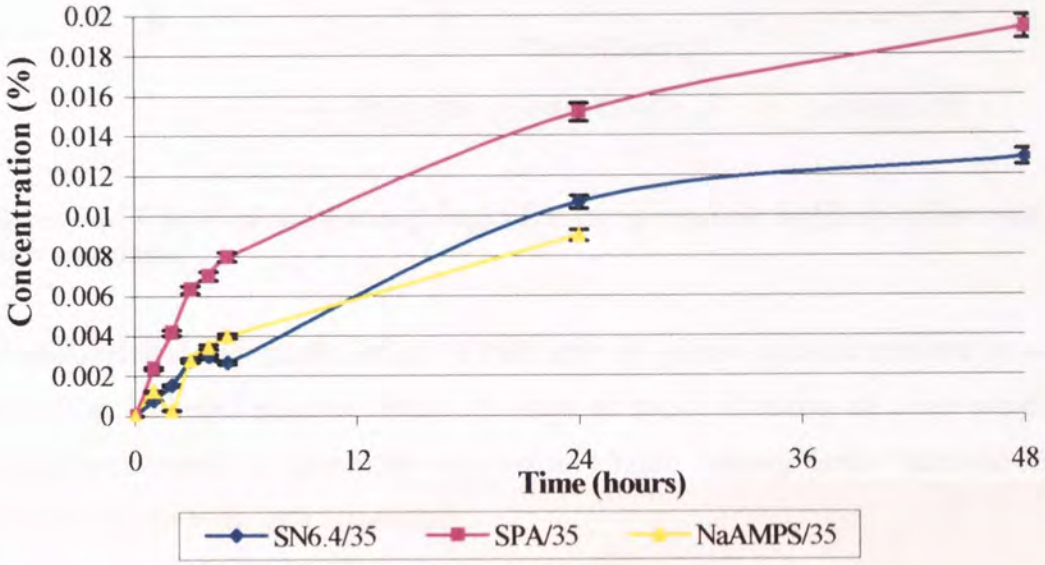


Figure 6.12 Cumulative release of ibuprofen from three hydrogel compositions into phosphate buffered saline

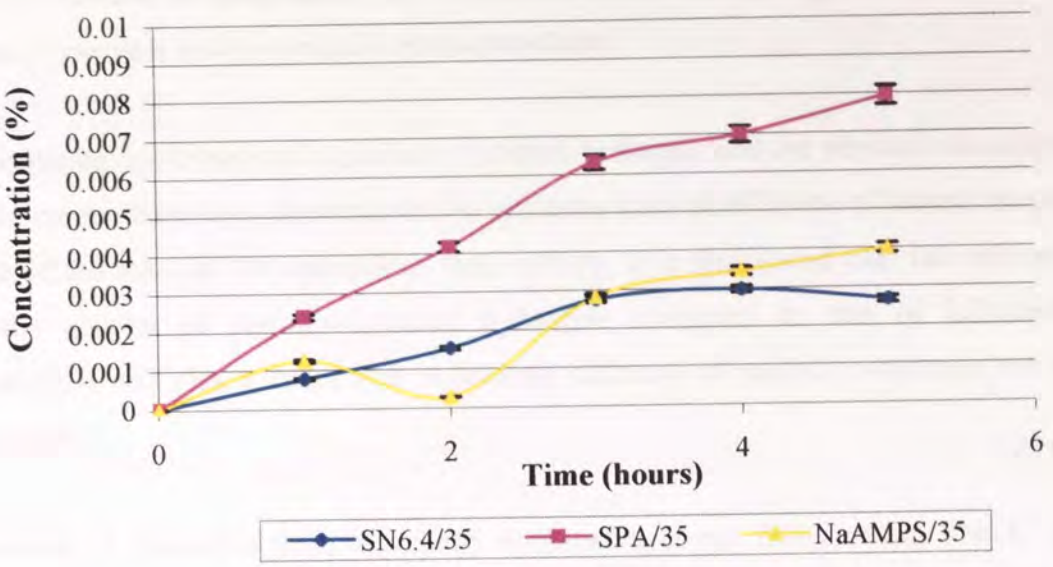


Figure 6.13 Cumulative release of ibuprofen into phosphate buffered saline over first 6 hours of release

As demonstrated previously, influx of PBS into the release systems resulted in swelling of all three hydrogel samples. Within the first 48 hours of release all three samples had swollen sufficiently to rupture the metricel membrane making further accurate study of release from the hydrogels impossible.

Closer examination of the first six hours of release that were measured shows release to have been greatest from the SPA homopolymer. Release concentrations from the SPA/NaAMPS copolymer and the NaAMPS homopolymer were similar at around half that seen for the SPA homopolymer.

Enhanced amide-sulphonate and amide-amide interchain hydrogen bonding between polar groups in the NaAMPS/SPA copolymer and the NaAMPS polymer respectively increased the effective crosslink density within these polymers. As partitioning of ibuprofen into PBS is diffusion controlled, as observed previously, the reduction in free space and mesh size of the polymers as a result of interchain hydrogen bonding slows down the release of the drug.

6.10.4 Release of ibuprofen from a partially hydrated hydrogel composition at two water contents into an organic release medium

Constituent monomers of a partially hydrated hydrogel, and the physical characteristics they confer, have been demonstrated to influence rates of diffusion of loaded compounds out of the material. In addition to these effects, it is anticipated that the reduced free water content of partially-hydrated hydrogels compared to that of fully-hydrated hydrogels will play a major role in limiting diffusion of loaded compounds out of the material.

Release of ibuprofen from a partially hydrated hydrogel composition; SN6.4, at two different water contents below the EWC of the composition was examined. Samples of the co-polymer, loaded with 2.5% ibuprofen acid, were produced at water contents of 25% and 35%. Release into Ethomeen solution (organic) was studied to determine the effect of water content of the hydrogel release vehicle on release characteristics.

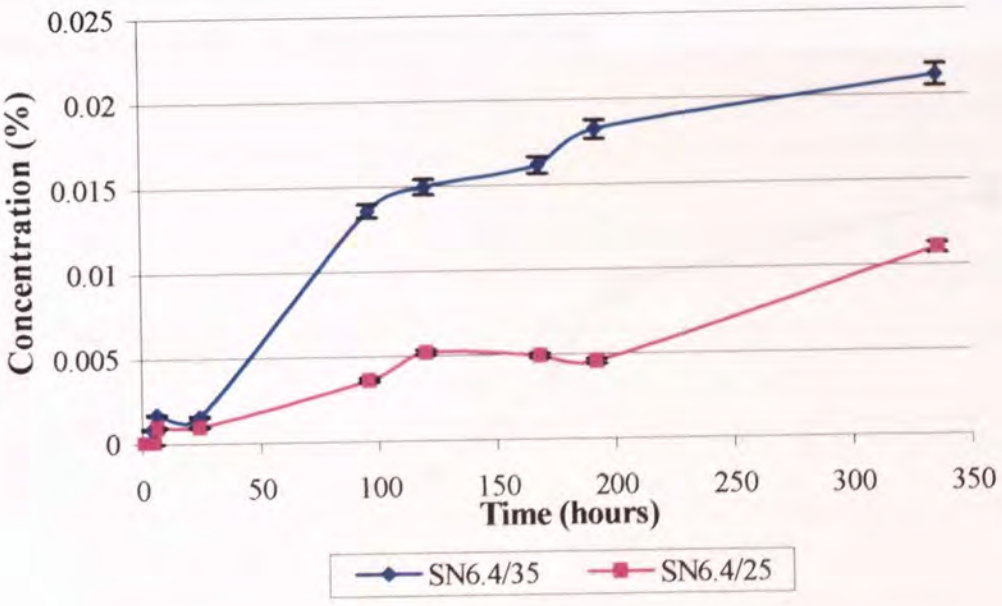


Figure 6.14 Cumulative release of ibuprofen from different water content hydrogels in to Ethomeen solution

Release of ibuprofen from the higher water content hydrogel was considerably greater than from the lower water content material. This can be considered as the result of a two-fold effect. Firstly, the positive partition coefficient of ibuprofen acid favours its partition

into a lipophilic environment. The increased hydrophilicity of the higher water content hydrogel pushed the equilibrium of the partitioning of the ibuprofen towards the lipophilic external release medium (Ethomeen solution) increasing release from this system. Secondly, diffusion of the drug through the lower water content gel is hindered by the reduction in availability of the transport medium, further slowing release of the drug from this polymer over extended release times.

6.10.5 Release of ibuprofen from a commercial partially hydrated hydrogel composition

Release of ibuprofen (5%) from a commercial partially hydrated hydrogel composition (composition details in table 6.1) was compared to release from the systems already studied. The commercial hydrogel composition chosen is quite different to those studied earlier in that an alternative plasticising solvent is used (see table 6.1 for composition details). Propane diol is more hydrophobic than glycerol and the effects of the change in hydrogel characteristics on release were examined.

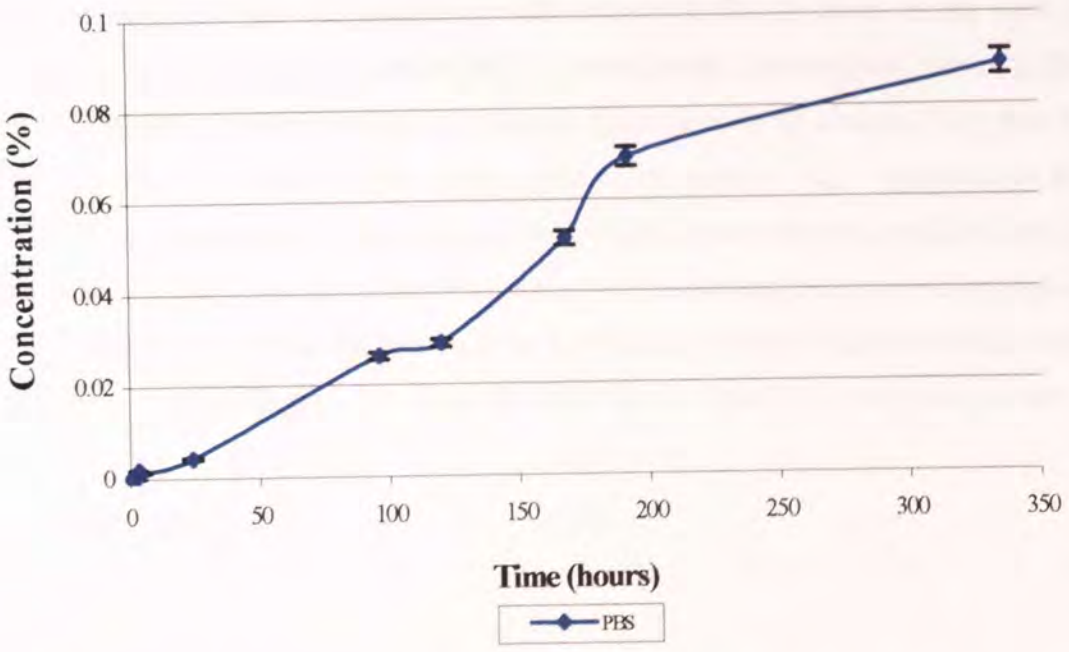


Figure 6.15 Cumulative release of ibuprofen from different a commercial skin adhesive hydrogel

Release into PBS from the commercial partially hydrated hydrogel confirms the importance of water in its role as a transport medium for the diffusion of solutes through a hydrogel. The significantly higher water content of the commercial hydrogel, 48%, compared to that of the hydrogels produced in this laboratory aids diffusion of ibuprofen thorough the hydrogel resulting in much greater release levels than would be expected as a result of the increased loading of this gel (section 5.7).

The principles of release and its underlying processes are the same for all samples despite any differences in composition. Specific release rates and the proportion of drug released during the different stages of the kinetic profile are determined by hydrogel composition.

6.10.6 Modelling release of drugs from hydrogels

The kinetic profiles observed for release of ibuprofen from partially hydrated hydrogels are quite different to those seen in studies of the release of fluorescein from fully hydrated hydrogels. This can be attributed to differences in the partition coefficients of both the hydrogel composition and the release compound. The reduced water content of partially hydrated hydrogels is associated with reduced diffusion rates. In the case of those systems where release is controlled by hydrophobic interactions however, the influence of hydrogel water content is reduced. Ibuprofen in its ionised form has an increased tendency to partition into octanol due to its positive $K_{o/w}$ compared to the ionised form of fluorescein. Though model compounds have been successfully used to provide a useful insight into the controlling factors of release and can give indications of the effects of solute properties on release from hydrogels, polymer-drug interaction must be investigated for specific drugs to obtain accurate release rates for a particular system.

6.11 Discussion

The kinetic profile of release from partially hydrated hydrogels includes a much reduced burst phase of release compared to that observed for release from fully hydrated hydrogels in chapter 5 of this thesis. The different method of production and loading of these materials, their reduced water contents and the presence of ionic groups in the constituent monomers were all shown to affect the loading capabilities of the materials and to influence release. The work within this chapter demonstrated a reduction in release as a result of interactions between the polar (ionic) forms of a drug and the ionic groups of constituent monomers. The reduced water content of the materials studied confirmed the dominant influence of diffusion on release from hydrogels, and indeed indicated diffusion to be the rate-controlling step for these release systems. The reduced free water content of these polymers is associated with a reduction in the availability of unbound loaded compound at the release surface of the gel. Release is dependent on the rate of diffusion of the compound through the polymer. Furthermore, incorporation of release compounds at the time of polymerisation may result in an increase in polymer-drug interactions than is observed in hydrogels loaded by imbibition.

The use of pigmented models to study release from partially hydrated hydrogels by colorimetric methods, as used in chapter 3 of this thesis, was unsuccessful. The need to maintain the pre-determined water content of partially hydrated hydrogels prevents loading of the gels by imbibition. Release compounds must be incorporated into the hydrogel at the time of polymerisation. The high absorbance of bromopyrogallol red and fluorescein block the transmission of UV light through samples, preventing photopolymerisation.

Inhibition of photopolymerisation was also a problem encountered during the loading of the hydrogels with ascorbic acid. The anti-oxidant properties of the compound reduce the availability of the free radicals that are essential for polymer chain propagation. Scavenging of the free radicals by the ascorbic acid molecules results in premature completion of the polymerisation reaction. Short polymer chains and the presence of unpolymerised residual monomer produces non-adhesive gels with poor cohesive properties and presents toxicity issues.

The simultaneous use of an oxidising agent (sodium metabisulphite) to counter these effects showed potential for the production of partially hydrated hydrogels loaded with ascorbic acid. Studies were carried out in the presence of equal concentrations of sodium metabisulphite and ascorbic acid. The high concentrations of ascorbic acid that are desirable in cosmeceutical applications may limit the use of this technique for loading with ascorbic acid. Detrimental effects of UV light on the therapeutic activity of ascorbic acid must also be examined before partially hydrated hydrogels produced by photopolymerisation can be considered as potential delivery vehicles for ascorbic acid.

A method for H.P.L.C analysis of ibuprofen in aqueous and organic media was developed and used to monitor release of the drug from a range of partially hydrated hydrogel compositions. Release studies examined the influence of polymer-drug interactions and hydrogel water content on release into aqueous and organic media.

The reduced water content of partially hydrated hydrogels promotes uptake of aqueous release media by the polymer. The presence of the imbibed drug changes the hydrophilic environment and alters the pH within the hydrogel. In some cases, flux of the medium into the hydrogels was so great that the swollen gel ruptured the supporting membrane between the gel and the release medium. This made further analysis of release from the system impossible.

Studies on release of ibuprofen into aqueous media at pH values either side of the pKa of ibuprofen demonstrated the effects of ionisation of the drug by the release medium on its extraction from the hydrogel. As seen for the release of fluorescein into aqueous media, extraction was much greater for the ionised form of the drug than for the non-ionised form of the drug. The positive water-octanol partition co-efficient of the ionised form of ibuprofen leads to increased extraction of the compound into aqueous media than was observed for the release of the ionised form of fluorescein. The difference in the partition co-efficients of the ionised forms of these compounds and its effect on their release prevents the use of fluorescein as a model for the release behaviour of ibuprofen.

Comparison with release into organic media confirmed the influence of water/octanol partition co-efficient on release from partially hydrated hydrogels. Release of the non-

ionised form of the drug (which has a positive water/octanol partition co-efficient) into Ethomeen:IPM solution was limited by the affinity of the compound for the lipophilic polymer backbone of the hydrogel.

The study of release from homopolymers and copolymers of NaAMPS and SPA developed during the work carried out in chapter 4 of this thesis demonstrated the effects on release of interchain hydrogen bonding (described in section 4.5.2). The increased tendency for interchain hydrogen bonding in SPA/NaAMPS copolymers and to a lesser extent in NaAMPS homopolymers effectively increases the crosslink density within the hydrogel and reduces mesh size. As release from hydrogel matrix systems is predominantly diffusion-controlled, the occurrence of interchain hydrogen bonding influences release of ibuprofen into both aqueous and organic release media.

A reduction of the water content of the hydrogel further demonstrated the controlling influence of diffusion of a solute through a hydrogel on release. The reduced availability of water as a transport medium produced the most significant reduction in release. A secondary effect of polymer-drug interactions increased partitioning of the non-ionised form of the drug out of the higher water content gel into the lipophilic medium over the extended release period.

Comparison of release from the partially hydrated hydrogels produced in this laboratory with release of ibuprofen form a pre-loaded commercial partially hydrated gel again demonstrated the influence of diffusion and therefore water content of the hydrogel on its release behaviour. Release from the higher water content commercial gel was much greater than from lower water content gels. This can be attributed in part to the higher loading level of the gel and the reduced hydrophilicity of the plasticising component used. The significantly higher water content of this hydrogel is however, likely to have played a key role in determining its release characteristics.

The work within this chapter has explored the controlling factors of release from partially hydrated hydrogels and demonstrated that drug ionisation, hydrogel composition and external release medium each play a role in determining the release characteristics of a hydrogel system. The information generated can be used as a guide for the optimisation

of release and gives some understanding of the limitations of partially hydrated hydrogels for controlled release applications.

On the basis of the understanding of the influence on release behaviour of hydrogel polymer and active compound and their interaction with each other which was established in this research, development of hydrogel release systems for specific drugs can now be pursued. Though the results of this work provide useful information regarding the general consideration and limitations of developing such systems, examination of kinetic profiles for specific systems is necessary to accurately predict release rates and to further increase our understanding of the mechanisms involved in release from partially hydrated hydrogels.

Chapter 7

Discussion and Suggestions for Further Work

7 Discussion of results

7.1 Overview

The work within this thesis involved studies of the parameters involved in the development of hydrogel release systems. The ability to produce a range of materials with good cohesive characteristics is an important foundation for the development of controlled release hydrogel systems. The roles of initiator and crosslinking system and hydrogel compositions in the production of cohesive partially hydrated hydrogels within this laboratory were identified and investigated.

A range of suitable monomers and optimum initiator/crosslinker systems for the production of hydrogels by photopolymerisation was realised. The potential for manipulation of hydrogel composition to modify both mechanical and diffusion properties of the material were explored, and parameter guidelines were established. These were then used to study release behaviour of hydrogels and how this could be controlled by modification of the hydrogel system.

The partitioning stages involved in the release of drugs from hydrogels into different release environments were examined and typical release profiles modelled with variations to controlling parameters. The potential for control and design of release by adjustment to hydrogel systems was studied to provide an outline of the broad potential of hydrogels as topical release systems.

7.2 Photopolymerisation of hydrogels

Empirical comparative studies of the relative suitabilities of monomers for photopolymerisation within this laboratory were conducted. A range of neutral monomers were polymerised in the presence of a photoinitiator used in the commercial production of hydrogel sheets. Polymerisation of the monomers in organic (and solvated) systems demonstrated those monomers with more hydrophilic

tendencies to polymerise more rapidly than those monomers with greater hydrophobic tendencies. The structures of these hydrophilic monomers, namely NNDMA, NVP, AMO and HEMA, promote the addition and propagation of a free radical, which in turn propagates polymerisation.

Polymerisation of these monomers in high polymer volume fraction solvated systems was not detrimental to polymerisation times or the degree of polymerisation achieved within this time. Indeed, a previously undocumented phenomenon was observed in the photopolymerisation of NVP in an aqueous system. NVP is well known for its low reactivity ratio in organic systems and this has been the key shortcoming of the monomer, limiting its use in hydrogel development. The presence of a low concentration of water in the system halved the time to polymerisation of the monomer compared to that observed for the organic system. The aqueous environment appears to facilitate an increased reactivity ratio of the monomer structure with the initiator/crosslinker system used. This result is promising for the use of water to aid faster polymerisation of selected monomers and as a plasticiser within hydrogels for skin adhesive applications.

Low polymer volume fraction solvated systems did not polymerise to produce cohesive hydrogels. Despite extended UV exposure times samples of all of the polymers contained a residual liquid component. Although increased sample thickness may have hindered effective transfer of UV light through the samples, it is likely that the presence of high solvent concentrations prevented the formation of long polymer chains and a cohesive polymer network.

More hydrophobic monomers (butyl acrylate, butyl methacrylate and vinyl butyrate) were not polymerised within experimentally feasible times in organic or solvated systems and as a result were not included in the portfolio of monomers carried through into subsequent studies into the development of skin adhesive hydrogels.

Minimisation of polymerisation time is an important factor for consideration in both the commercial production of hydrogel sheets and for experimentally feasible hydrogel development within this laboratory. Comparison of the photoinitiator system used in the commercial production of hydrogel sheets (Irgacure 184) with alternative

photoinitiator systems confirmed the suitability of the current system for this application. Trials using two initiator systems used in the curing of polymer coatings for food can linings proved unsuccessful. Problems with the solubility of the initiators in the sample compositions prevented the use of these initiators in further studies.

Ladder studies showed reduced polymerisation times for the monomers in organic and solvated systems with increasing concentrations of Irgacure 184. Improvements in polymerisation times were pronounced with an increase of between 0.1% and 0.5% Irgacure 184 above the concentration that is currently used commercially. This highlights the importance of consideration of individual laboratory conditions, duration of exposure and light intensity, as well as photoinitiator system, in the photopolymerisation of hydrogels.

During photopolymerisation of hydrogel sheets a small amount of thermal energy is generated by the UV source. Usually this energy is simply wasted, as it cannot be used by photoinitiators to produce free radicals. The use of this energy to further reduce polymerisation times by inclusion of a thermal initiator system in the monomer sample was studied. The presence of potassium persulfate, at concentrations matching those used in the ladder study for optimisation of Irgacure 184, failed to produce the same improvement in polymerisation times for organic or solvated systems.

The identification, during these preliminary studies, of those monomers susceptible to photopolymerisation and the most effective initiator system for polymerisation of these monomers formed the basis for subsequent research into the production of partially hydrated hydrogels for dermal applications by photopolymerisation.

7.3 Partially hydrated ionic hydrogels

The ability to manipulate the adhesive and cohesive properties of partially hydrated hydrogels is desirable in their development for skin contact applications, in particular for their use as topical release systems. Interaction of three key components of the hydrogel composition is considered to control this behaviour:

-The rheological properties of a hydrogel determine its viscoelastic behaviour at the time of application of the device, during the functional lifetime of the device and at the time of its removal.

-A hydrophilic component within the polymer backbone of the hydrogel confers a high equilibrium water content (EWC) which results in the removal of the interfacial water layer between the hydrogel and the skin by partially hydrated hydrogels.

-Hydrophobic domains in the polymeric component of the hydrogel interact with skin lipids to promote adhesive bond formation.

Modification of partially hydrated hydrogel systems to alter their adhesive performance was explored and the effects of changes to hydrogel composition and crosslinking systems on the properties of the hydrogels were examined. The influence of monomer, water, glycerol and crosslinking system on hydrogel behaviour was examined. The aim of this exploratory work was to identify the parameters for manipulation of hydrogel compositions. Topical and transdermal release capabilities of partially hydrated hydrogel systems within these parameters could then be examined.

Adhesive performance was assessed by measurement of the adhesive and dynamic mechanical behaviour of the hydrogel. Rheological measurement of viscoelastic responses at different stress frequencies gave information about hydrogel behaviour during application and removal. Peel strength testing was used to measure the skin adhesive properties of the hydrogels.

Polymerisation studies were designed to investigate the possibility of using monomer combinations that would influence the release characteristics of the hydrogels by modifying their hydrophobic and ionic nature. Copolymers of the ionic monomers SPA and NaAMPS have previously been successfully used in the production of partially hydrated hydrogel sheets for commercial applications. The copolymerisation of a range of neutral monomers with these ionic monomers under typical moving web photopolymerisation conditions formed the basis of experimental studies.

The concentration and nature of the crosslinking system used in the photopolymerisation of partially hydrated hydrogels play an important role in controlling the rheological and adhesive properties of the hydrogel. An increase in crosslink density is associated with increasing cohesive strength of the hydrogel. This can be achieved by the use of increased concentrations of a crosslinking agent or by use of multifunctional crosslinking systems.

The difference in behaviour of bifunctional (Ebacryl II) and trifunctional (PETA) crosslinking systems was demonstrated with wholly ionic monomer systems. SPA: NaAMPS hydrogels prepared with the bifunctional crosslinking system at baseline levels showed excellent adhesive properties whereas the same gels produced in the presence of the trifunctional system were stiffer and showed poor adhesion

Copolymers of ionic monomers with neutral monomers were much less cohesive than the wholly ionic systems when polymerised in the presence of the bifunctional crosslinking system. The use of a trifunctional crosslinking system improved the cohesiveness of the gels but did not fully overcome the shortcomings of the ionic-neutral copolymer combinations.

The observed difference between NaAMPS and SPA copolymers polymerised in the presence of bifunctional crosslinking agent became insignificant when PETA was used. This is a function of the greater interchain cohesion facilitated by the trifunctional crosslinker. Dipolar and hydrogen bonding between the amide and sulfonate groups of the ionic monomers produces greater interchain cohesivity. A similar result was observed in the mechanical properties of copolymers of the ionic monomers at differing ratios. Improvement in mechanical properties was associated

with an increase in SPA content to around 30%, consistent with the enhancement of sulfonate-amide interchain links by the increasing availability of sulfonate group.

The effects of monomer composition were shown to be a function of several factors. The structure of the copolymers was governed by rates of polymerisation and reactivity ratios of the constituent monomers whereas monomer hydrophilicity and solvent power affected copolymer function in terms of diffusion properties. Preliminary studies in chapter three of this thesis together with general principles of monomer structure are of help in explaining the observed reactivity ratios of the monomers studied. In terms of rate of homopolymerisation in aqueous solution, the ionic monomer NaAMPS, an acrylamide derivative, is expected to be fastest and the ionic acrylate SPA somewhat slower. Although *N,N*-dimethyl acrylamide and *N*-acryloyl morpholine are acrylamide derivatives, the steric hindrance of the *N*-substituents has a marked effect in reducing polymerisation rates which are appreciably slower in aqueous solution than those of NaAMPS and SPA. *N*-Vinyl pyrrolidone is unusual in that its rate of polymerisation in aqueous solution is appreciably faster than in bulk or organic solution, although still slower than that of the ionic monomers.

Rates of copolymerisation of the ionic monomers with neutral monomers appeared to be a function of homopolymerisation rates of the monomers. As no unusual cross-reactivity effects were observed any residual or unpolymerised monomer in the ionic-neutral copolymers will be predominantly neutral monomer. This was shown to produce an unusual effect that is not seen in the ionic systems. The ability of the neutral monomers to act as solvents for their respective homopolymers gave them some ability to swell their 50:50 copolymers. This effect is a likely contributor to the reduced cohesivity of the ionic-neutral copolymers. The observed differences between the 50:50 copolymers studied may be a result of the solvating effects of residual monomer rather than the structure of the polymer, suggesting that optimisation of polymerisation conditions and reducing neutral monomer proportions within the copolymer might produce a range of effective skin adhesive hydrogels.

7.4 Release of model compounds

Hydrophilic molecules are readily loaded into and diffuse out of hydrogels. Coupled with their exceptional biocompatibility this makes hydrogels an obvious consideration as vehicles for drug delivery. The ease with which molecules diffuse out of hydrogels has however led to speculation surrounding the ability to control release. Work within this thesis investigated the partitioning stages involved in release from hydrogels and the ways in which influencing factors can be altered to modify and control release.

Model compounds were used to establish release profiles of typical hydrogel compositions. These showed that an initial rapid burst of release of a solute from a hydrogel does indeed occur. This is followed by a second phase of approximate first order release. During this period it would appear that the ratio of release is proportional to the concentration of remaining material. A portion of the loaded compound is retained by the hydrogel or released at an infinitesimally slow rate dependent on release conditions.

Ideally a controlled release device will supply a drug at a constant rate equal to its rate of absorbance/elimination from the delivery site, independent of the amount of drug remaining in the device. This is known as zero-order release. Release of a compound from a controlled release device is usually however slower than absorption of the compound across cell membranes and as such is the rate-limiting step. The burst phase of release from hydrogels provides an initial reservoir of the drug at the delivery site, which is subsequently maintained by the second phase of release. This ensures that release rate is never a limiting factor. This profile of release is particularly useful in applications such as wound dressings in which an initial high dose would be desirable.

Initial loading concentration was demonstrated not to alter this release profile but increased the amount of compound released. The increased release was especially pronounced in the initial burst phase of the release profile.

The relative hydrophilicity of the polymer backbone of a hydrogel is important in its affinity for a loaded compound. The use of hydrogels with polymer backbones of differing hydrophilicity can influence both the maximum loading capacity of the hydrogel and its release kinetics. Studies with hydrogels of differing hydrophilicity demonstrated the effects of polymer-drug interactions on release of a compound. A hydrophobic compound (bromopyrogallol red) was released more readily into an aqueous medium from a more hydrophilic hydrogel. Modification of hydrogel composition to include polymeric components of greater or lesser hydrophilicity can be used to regulate release for an intended application.

The partitioning stages involved in the release of a drug from a hydrogel to a delivery site are a combined result of hydrogel, drug and release environment characteristics. The pH of the hydrogel will influence the degree of ionisation of a loaded compound. This in turn will affect its partitioning between the aqueous and polymeric components of the hydrogel. Release of a compound from the aqueous component will depend on the nature of the release environment and the partition coefficient of the compound. The cumulative effect of each of these stages determines the delivery profile of the compound. Examination of the influence of each of the partitioning stages identified the capacity for modification of release of a compound by manipulation of the different components of the release system.

The pH of external aqueous release media determines the pH of the release site. Depending on its pKa this alters the degree of ionisation of the loaded compound here. Subsequent release of the ionised form of a compound into aqueous media, at a pH above the pKa of the loaded compound, was greater than release of the compound in its non-ionised form. The greater solubility of the ionised form of the compound (more negative diffusion coefficient) resulted in a two-fold increase in the size of the burst phase of release compared with that of the non-ionised form of the compound. The contribution of a secondary effect of interactions between the compound and the polymer backbone will be a major influence on the second stage of release of the compound. Increased polymer-compound interactions by the acid form of the drug limit release into aqueous media below the pKa of the compound. In contrast, the hydrophilic nature of the ionised form of the drug favours its continued partition into the aqueous release environment.

The influence of the pH of the release environment on the release of a compound from a hydrogel is important with respect to the difference in pH at various delivery sites. Experimental studies of the effects of release medium pH provide indications of the likely release behaviour of compounds at specific delivery sites.

The ability of a release medium to alter release by ionisation of a compound was studied. Both ionised and acid forms of a model compound were loaded into hydrogels and their release into aqueous media at pH either side of the pKa of the compound was compared. Conversion of the ionised form of the compound into an acid for release into aqueous media (pH4) was not complete and as a result its release into pH4 buffer was not as extensive as release when the acid form of the compound was loaded into the hydrogel and released into pH 4 buffer.

The effects of solubility of a compound on its release suggest that non-ionised forms of a compound might be more readily extracted from a hydrogel into an organic medium than into an aqueous medium. In the presence of a lipophilic release environment competition exists between the polymer backbone of the hydrogel and the release medium for the non-ionised form of a compound. Studies of release into octanol were used to examine the extent of this competition and its effect on release for the ionised form of a comopound. Though the competition between the hydrogel and octanol was not fully explained by these results, the difference in release provides important information as to how the release system may behave at the relatively hydrophobic environment of human skin. The combination of both a lipophilic component (skin lipids) and an aqueous component (sweat) at the skin surface at a pH of around 5 is likely to induce release behaviour somewhere in-between that seen with the octanol and pH4 systems studied.

The inability of organic media to change the pH at the release site and as such the ionisation of a loaded compound is an important consideration for release to lipophilic delivery sites. Whereas aqueous media were demonstrated to ionise a compound to favour its solubility in the medium, release rates into octanol were pre-determined by the ionisation state of the compound at the time of loading.

Release work with model compounds demonstrated a variety of controlling mechanisms for release from hydrogels. Interaction of these parameters determines release rates for the system. Experimental kinetic profiles indicate the degree of influence of each of the parameters and can be used as indicators for areas for modification of a release system for manipulation of release to achieve desired delivery rates.

7.5 Loading and release from partially hydrated ionic hydrogels

The adhesive properties of partially hydrated hydrogels makes them an obvious choice for topical and transdermal delivery of drugs and cosmeceuticals. The extended application time afforded by their adhesive properties is favourable for the delivery of therapeutically effective levels of topical actives and administration of systemic drugs via the skin avoids the problems of first pass metabolism of drugs that occurs in oral delivery systems.

The effect of the reduced water content of partially hydrated hydrogels was shown to be the dominant factor in controlling diffusion and release of solutes from the polymers. Polar interactions between ionised compounds and the ionic groups of the constituent monomers of partially hydrated hydrogels also influence release.

In order to maintain the pre-determined water content of partially hydrated hydrogels, release compounds must be incorporated into the hydrogel at the time of polymerisation. This method of loading has obvious advantages in terms of accurate control of loading levels but is subject to limitations; pigmented compounds cannot be loaded into the materials under the photopolymerisation conditions studied and supplementary initiator systems were required for polymerisation in the presence of compounds with antioxidant capabilities. The detrimental effects of UV light on the therapeutic activity of some drugs must also be considered.

The capacity of partially hydrated hydrogels to absorb large amounts of additional water results in swelling of the gels by aqueous release media. The accompanying

change in the pH within the hydrogel to that of the release medium may result in ionisation of the compound depending on its pKa. As observed in chapter 5 of this thesis, the increased solubility of ionised forms of a compound (more negative water/octanol partition coefficient) in aqueous media increases release from these systems.

The more hydrophobic nature (more positive water/octanol partition coefficient) of the unionised form of a compound creates competition between the polymer backbone and lipophilic extraction media. Release of the compound in these conditions is a function of both polymer-drug interactions and the water content (hydrophilicity) of the hydrogel.

The polar groups of the ionic monomers of partially hydrated hydrogels interact with release compounds in their ionised form. Modification of the polar (ionic) component of the hydrogel can be used to manipulate polymer-drug interactions and as a result, release.

The reduction in free water available for diffusion of a release compound through a partially hydrated hydrogel, together with increased polymer-drug interactions, greatly reduces the burst phase of release from these polymers. Such control over the initial delivery rates of a compound are desirable in many controlled release applications, indeed it has been the misconception of the inability to control this burst release which has previously limited the development of hydrogels as drug delivery systems.

Modification of the water content and hydrophilicity of partially hydrated hydrogels associated with their constituent plasticising components provides a further mechanism for the control of release over extended periods.

The results of this chapter of work have provided valuable information for the future design of partially hydrated hydrogel drug delivery systems for dermal applications. The demonstrated ability to manipulate and control release from these polymers is promising for their potential use in clinical and cosmetic applications.

7.6 Concluding summary

The understanding of the controlling factors of hydrogel properties and release behaviour established in this work provides a basis for the development of partially hydrated hydrogels for dermal release applications. Identification of successful monomer, crosslinker and initiator compositions and their individual role in the adhesive, cohesive and dynamic mechanical properties of a hydrogel allows the selection of feasible hydrogel compositions for release studies. Observed release behaviour and examination of its controlling factors enables the prediction of the likely loading and release characteristics of a chosen hydrogel composition. In the development of a hydrogel for a release application the most acceptable compromise in terms of polymerisability, gel properties and release characteristics can be chosen using these fundamental patterns of behaviour. This avoids the necessity to optimise polymerisation and release characteristics of a broad range of compositions for each new application.

7.7 Suggestions for future work

Many possibilities exist for the extension of this investigation into the principles controlling the adhesive and release properties of hydrogels produced by photopolymerisation. The work within this thesis examined several areas considered and subsequently proven to be important in determining the properties of hydrogels. The purpose of this research was to overview the principles involved in the development of hydrogels for dermal applications and, more specifically, as release vehicles. The information provided by this program of research provides the basis for the optimal design of hydrogels for specific dermal release applications and some understanding of the limitations of these systems for controlled release applications. Potential extensions for the parameters studied and broader influences which might be considered in the development of topical hydrogel release systems are detailed.

The capability to produce hydrogels with desired adhesive and cohesive properties and dynamic mechanical behaviour for clinical use is an essential starting point for the development of hydrogels for dermal applications. Further examination of the use of thermal/redox initiator systems in the photopolymerisation of hydrogels is suggested with an increase in the range of monomers suited to this production technique in mind.

Reduction of the proportion of neutral monomer used in ionic-neutral copolymers has shown potential for the development of a range of very effective skin adhesive gels. Now that the release profiles of these copolymers have been examined and the suitability of the materials for use in release applications confirmed, potential exists for further manipulation of both adhesion and release characteristics by alteration of the ratio of ionic to neutral monomer within the gels.

The observed increased reactivity ratio of NVP in aqueous solution than is generally associated with polymerisation of the monomer in bulk and organic systems indicates the potential for use of this monomer in the production of partially hydrated hydrogels for dermal applications. Further exploration of the benefits of including this neutral monomer within hydrogels for a wide range of applications is now a feasible proposal that needs to be explored.

Comparison of gels produced within this laboratory with a commercial partially hydrated hydrogel highlighted the role of the hydrophilicity of humectants used in hydrogel compositions on the ability of the material to absorb aqueous media. Further investigation of the effects of alternative humectants/plasticisers to glycerol (as used in this research) are necessary to establish a better understanding of the principles involved in the influence on both release and mechanical properties of partially hydrated hydrogels by this phase of the composition.

The production of partially hydrated hydrogels by free radical polymerisation in the presence of photoinitiators and crosslinkers is associated with the potential for the existence of unpolymerised monomer and unused initiator/crosslinking agents within the hydrogel produced. Many of these compounds are toxic in their unpolymerised form and must be removed from the gel prior to its clinical use. In the case of fully

hydrated hydrogels, residuals are simply "washed" out of the gel using solvents however the desire to control the water content of partially hydrated hydrogels prevents the use of this technique. Studies into the reduction/elimination of residuals by adjustment of initiator/crosslinker conditions, and toxicity tests of polymerised materials must be carried out to confirm the suitability of these materials for clinical applications.

The effects of increase in crosslink density, by increasing crosslinking monomer concentration and by the use of multifunctional crosslinking agents, on the mechanical properties of hydrogels have been established. It is known that release of a compound from a hydrogel is controlled by its diffusion through the gel, itself a function of several parameters including crosslink density and associated mesh size. Release rates for specific drug-polymer systems might be desirably controlled by changes to the crosslink density within the hydrogel.

On the basis of the understanding of the influence on release behaviour of hydrogel polymer and active compound and their interaction with each other which was established in this research, development of hydrogel release systems for specific drugs can now be pursued. Though the results of this work provide useful information regarding the general consideration and limitations of developing such systems, examination of kinetic profiles for specific systems is necessary to accurately predict release rates and to further increase our understanding of the mechanisms involved in release from partially hydrated hydrogels.

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Appendices

Appendices

Appendix I

Variation in polymer and water volume fraction

SPA/NaAMPS (50:50) %(w/w)	Water %(w/w)	Glycerol %(w/w)	Ebacryl/Irgacure (10:3) %(w/w)	N° passes through UV	G' (1Hz)	G" (1Hz)	tan delta (1Hz)	G' (10Hz)	G" (10Hz)	tan delta (1Hz)
30	45	25	0.33	5	8.1925E+02	2.1811E+02	2.6869E-01	1.7229E+03	3.0849E+02	1.7609E-01
35	40	25	0.33	4	2.2020E+03	4.9856E+02	2.2638E-01	3.4943E+03	9.4879E+02	2.7257E-01
40	35	25	0.33	5	3.9645E+03	8.0693E+02	2.0355E-01	5.8409E+03	1.4917E+03	2.5537E-01
45	30	25	0.33	4	4.7495E+03	1.3688E+03	2.8843E-01	7.6775E+03	2.6137E+03	3.4087E-01
50	25	25	0.33	3	6.6477E+03	2.3717E+03	3.5709E-01	1.1517E+04	5.1323E+03	4.4459E-01
55	20	25	0.33	1	8.1716E+03	3.1525E+03	3.8760E-01	1.4555E+04	8.6644E+03	5.9565E-01
20	35	45	0.33	5	4.0043E+02	1.1782E+02	2.9417E-01	6.0069E+02	2.0292E+02	3.4125E-01
25	35	40	0.33	5	4.7914E+02	2.3240E+02	4.8680E-01	1.3007E+03	4.3676E+02	3.4622E-01
30	35	35	0.33	3	9.4974E+02	4.1348E+02	4.3663E-01	1.8586E+03	7.4969E+02	4.0608E-01
35	35	30	0.33	3	1.7048E+03	5.5991E+02	3.2831E-01	3.1946E+03	9.0840E+02	2.8952E-01
40	35	25	0.33	5	3.9645E+03	8.0693E+02	2.0355E-01	5.8409E+03	1.4917E+03	2.5537E-01
45	35	20	0.33	3	6.3060E+03	1.1687E+03	1.8597E-01	8.5960E+03	2.3978E+03	2.7924E-01
50	35	15	0.33	3	6.3853E+03	1.5667E+03	2.4566E-01	1.0160E+04	3.8122E+03	3.7547E-01
55	35	10	0.33	3	1.0462E+04	2.6389E+03	2.5303E-01	1.8937E+04	8.3416E+03	4.3946E-01
60	35	5	0.33	2	2.0401E+04	8.4852E+03	4.0543E-01	4.6725E+04	2.6661E+04	5.6289E-01

Ionic copolymers

SPA % (w/w)	NaAMPS % (w/w)	Water %(w/w)	Glycerol %(w/w)	Ebacryl/Irgacure (10:3) %(w/w)	G' (1Hz)	G" (1Hz)	tan delta (1Hz)	G' (10Hz)	G" (10Hz)	tan delta (1Hz)
0	100	30	30	0.33	3.9971E+02	1.3089E+02	3.2677E-01	9.6178E+02	1.7426E+02	1.8381E-01
25	75	30	30	0.33	4.4394E+03	9.8639E+02	2.2229E-01	6.6310E+03	2.0981E+03	3.1626E-01
37.5	62.5	30	30	0.33	5.5952E+03	9.3208E+02	1.6656E-01	7.4585E+03	1.9760E+03	2.6470E-01
50	50	30	30	0.33	3.8645E+03	7.6185E+02	1.9794E-01	5.7343E+03	1.4604E+03	2.5501E-01
60	40	30	30	0.33	3.9645E+03	8.0693E+02	2.0355E-01	5.8409E+03	1.4917E+03	2.5537E-01
62.5	37.5	30	30	0.33	2.2570E+03	5.2827E+02	2.3407E-01	4.0102E+03	6.0102E+02	1.5094E-01
75	25	30	30	0.33	1.8820E+03	5.0890E+02	3.2437E-01	3.8209E+03	8.3039E+02	2.2026E-01
100	0	30	30	0.33	1.7419E+03	5.3856E+02	3.0881E-01	3.0820E+03	9.0419E+02	2.9267E-01

Ionic/neutral copolymers

Copolymer	Monomer (50:50) % (w/w)	Water %(w/w)	Glycerol %(w/w)	PETA/Irgacure (5:3) % (w/w)	G' (1Hz)	G" (1Hz)	tan delta (1Hz)	G' (10Hz)	G" (10Hz)	tan delta (1Hz)
NaAMPS/NNDMA	40	30	30	0.33	6.2587E+03	1.4644E+03	2.3399E-01	1.1051E+04	2.9510E+03	2.6704E-01
NaAMPS/AMO	40	30	30	0.33	4.3784E+03	8.0330E+02	1.8347E-01	6.5981E+03	1.4574E+03	2.2088E-01
SPA/NNDMA	40	30	30	0.33	5.5955E+03	8.7038E+02	1.5555E-01	7.6909E+03	1.8995E+03	2.4699E-01
SPA/AMO	40	30	30	0.33	4.9975E+03	7.0153E+02	1.4038E-01	6.6911E+03	1.5817E+03	2.3639E-01

Appendix II

Release of bromopyrogallol red

	Cumulative release (% concentration)				Cumulative release (% concentration)	
	BPR (saturated)		BPR (1%)		BPR (saturated)	
Time (hours)	HEMA contact lens	MMA/NVP contact lens	HEMA Contact lens	Time (hours)	HEMA:AMO membrane	HEMA:NVP membrane
0	0	0	0	0	0	0
1	0.0013	0.00083	0.00026	1.5	0.00045	0.00028
2	0.00141	0.00164	0.00032	4.5	0.00079	0.00053
4	0.001505	0.00233	0.00041	27.5	0.00123	0.00103
6	0.001585	0.00273	0.000475	142.5	0.001564	0.0015
16	0.00175	0.00373	0.000635	287.5	0.001609	0.00168
50	0.001855	0.00423	0.000685	431.5	0.001649	0.00178
73	0.00194	0.004445	0.000725	575.5	0.001674	0.00186
97	0.00201	0.004605	0.00076			
180	0.002075	0.004795	0.000785			
216	0.002098	0.004945	0.000804			
266	0.002118	0.005045	0.000819			
336	0.002136	0.005125	0.000833			
409	0.002154	0.005205	0.000843			
504	0.002169	0.00527	0.000852			

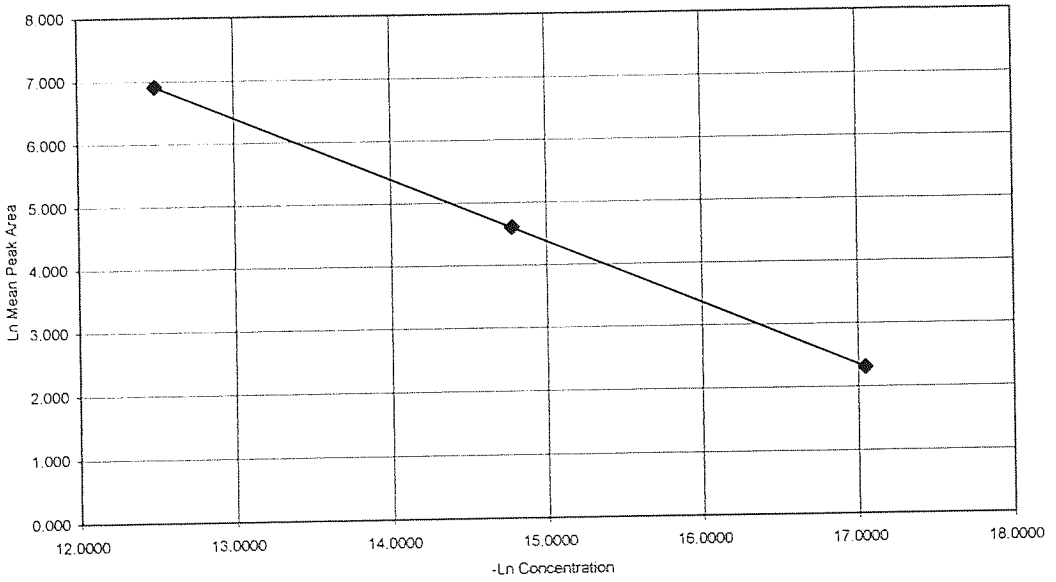
Release of fluorescein and sodium fluorescein

Fluorescein				
	HEMA		HEMA/NVP	
Time (hrs)	PBS	pH4	PBS	pH 4
1	0.133	0.05	0.227	0.05
2	0.15	0.074	0.321	0.06
3	0.159	0.086	0.395	0.065
4	0.165	0.092	0.454	0.07
5	0.17	0.095	0.458	0.075
6	0.172	0.098	0.489	0.078
8	0.175	0.1	0.497	0.08
10	0.176	0.105	0.503	0.082
24	0.177	0.11	0.503	0.088
26	0.177	0.11	0.503	0.088
36	0.177	0.115	0.503	0.092
48	0.177	0.116	0.503	0.093
72	0.177	0.119	0.503	0.095

Fluorescein (sodium salt)						
	HEMA			HEMA/NVP		
Time (hrs)	Octanol	PBS	pH4	Octanol	PBS	pH4
1	0.006	0.001	0	0.006	0.005	0.004
2	0.006	0.001	0	0.006	0.005	0.006
3	0.006	0.001	0.003	0.006	0.005	0.008
4	0.006	0.001	0.005	0.006	0.005	0.008
5	0.006	0.001	0.007	0.006	0.005	0.01
6	0.006	0.001	0.008	0.006	0.005	0.01
8	0.006	0.001	0.008	0.006	0.005	0.01
10	0.006	0.001	0.008	0.006	0.005	0.01
24	0.006	0.001	0.008	0.01	0.005	0.01
26	0.006	0.001	0.008	0.01	0.005	0.01
36	0.006	0.001	0.008	0.01	0.006	0.01
48	0.006	0.001	0.008	0.01	0.006	0.01
72	0.006	0.001	0.008	0.01	0.006	0.01

Appendix III

Calibration curve for ibuprofen



Mean peak areas of ibuprofen release samples

SN6.4/35 ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	0.999624653	2.92771E-05
3	0.999300508	5.45604E-05
4	0.989199427	0.000842445
5	0.989487778	0.000819953
6	0.978283739	0.001693868
24	0.979784725	0.001576791
96	0.825838692	0.013584582
120	0.808242789	0.014957062
168	0.792768682	0.016164043
192	0.766317441	0.01822724
336	0.728826209	0.021151556

SN 6.4/35 PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.990007409	0.000779422
2	0.980243863	0.001540979
3	0.96467407	0.002755423
4	0.961880196	0.002973345
5	0.965742865	0.002672057
24	0.863067393	0.010680743
48	0.835160527	0.012857479
120	0.85311324	0.011457167
148	0.877608953	0.009546502
172	0.898807025	0.007893052

SN 6.4/35 pH4		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	0.999999437	0.000371684
4	0.999986899	0.000552666
5	0.999695325	2.37646E-05
6	0.992914543	1.02188E-06
24	0.995234825	4.39408E-08
48	0.999999976	1.88945E-09

SPA ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.988215716	0.000942743
24	0.974337645	0.002052988
96	0.88831421	0.008934863
120	0.852849248	0.01177206
168	0.796637173	0.016269026
192	0.801989612	0.015840831
336	0.713592234	0.022912621

SPA PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.959619174	0.002382469
2	0.929444277	0.004162788
3	0.892804841	0.006324514
4	0.8814192	0.006996267
5	0.865085499	0.007959956
24	0.743042962	0.015160465
48	0.672514895	0.019321621

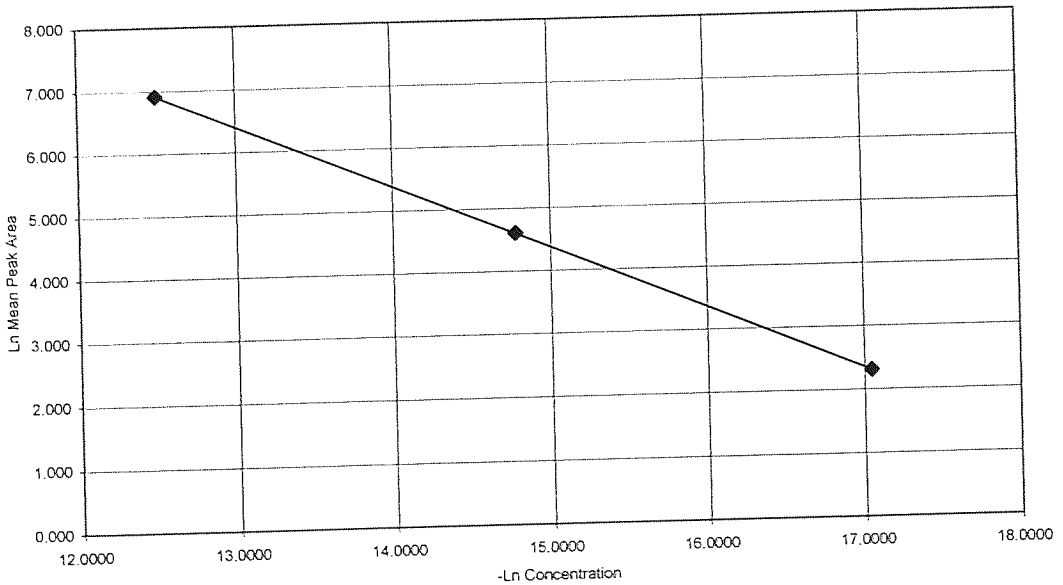
NaAMPS ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.999693427	1.16498E-05
24	0.947460266	0.00199651
96	0.968069644	0.001213354
120	0.938950162	0.002319894
168	0.917968717	0.003117189
192	0.813481157	0.007087716
336	0.756700845	0.009245368

NaAMPS PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.963517016	0.001240421
2	0.991863632	0.000276637
3	0.917137077	0.002817339
4	0.898519286	0.003450344
5	0.882456485	0.003996479
24	0.734970915	0.009010989

SN6.4/25 ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.98484144	0.000954989
24	0.984827622	0.00095586
96	0.942832492	0.003601553
120	0.917296804	0.005210301
168	0.921794163	0.004926968
192	0.927396266	0.004574035
336	0.82540371	0.010999566

Appendix IV

Ln mean peak area Vs -Ln Ibuprofen concentration for standards



Mean peak areas

SN6.4/35 ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	0.999624653	2.92771E-05
3	0.999300508	5.45604E-05
4	0.989199427	0.000842445
5	0.989487778	0.000819953
6	0.978283739	0.001693868
24	0.979784725	0.001576791
96	0.825838692	0.013584582
120	0.808242789	0.014957062
168	0.792768682	0.016164043
192	0.766317441	0.01822724
336	0.728826209	0.021151556

SN 6.4/35 PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.990007409	0.000779422
2	0.980243863	0.001540979
3	0.96467407	0.002755423
4	0.961880196	0.002973345
5	0.965742865	0.002672057
24	0.863067393	0.010680743
48	0.835160527	0.012857479
120	0.85311324	0.011457167
148	0.877608953	0.009546502
172	0.898807025	0.007893052

SN 6.4/35 pH4		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	0.999999437	0.000371684
4	0.999986899	0.000552666
5	0.999695325	2.37646E-05
6	0.992914543	1.02188E-06
24	0.995234825	4.39408E-08
48	0.999999976	1.88945E-09

SPA ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.988215716	0.000942743
24	0.974337645	0.002052988
96	0.88831421	0.008934863
120	0.852849248	0.01177206
168	0.796637173	0.016269026
192	0.801989612	0.015840831
336	0.713592234	0.022912621

SPA PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.959619174	0.002382469
2	0.929444277	0.004162788
3	0.892804841	0.006324514
4	0.8814192	0.006996267
5	0.865085499	0.007959956
24	0.743042962	0.015160465
48	0.672514895	0.019321621

NaAMPS ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.999693427	1.16498E-05
24	0.947460266	0.00199651
96	0.968069644	0.001213354
120	0.938950162	0.002319894
168	0.917968717	0.003117189
192	0.813481157	0.007087716
336	0.756700845	0.009245368

NaAMPS PBS		
time	Co-C/Co	Concentration (%)
0	1	0
1	0.963517016	0.001240421
2	0.991863632	0.000276637
3	0.917137077	0.002817339
4	0.898519286	0.003450344
5	0.882456485	0.003996479
24	0.734970915	0.009010989

SN6.4/25 ethomeen		
time	Co-C/Co	Concentration (%)
0	1	0
1	1	0
2	1	0
3	1	0
4	1	0
5	1	0
6	0.98484144	0.000954989
24	0.984827622	0.00095586
96	0.942832492	0.003601553
120	0.917296804	0.005210301
168	0.921794163	0.004926968
192	0.927396266	0.004574035
336	0.82540371	0.010999566